

**SYNTHESIS AND DIVERSIFICATION OF BRIDGED *N*-HETEROCYCLES VIA  
SEQUENTIAL TRANSITION METAL-CATALYZED REACTIONS**

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Submitted to the graduate degree program in Chemistry and the Graduate Faculty of the  
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## Abstract

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Of major interest to modern synthetic organic chemistry is the use of transition metal catalysis to achieve carbon-carbon bond formation. Over the past 40 years many of these versatile and simple methodologies have been developed including the Heck reaction, Stille coupling, Suzuki coupling, Sonogashira coupling, Buckwald-Hartwig reaction, Tsuji-Trost reaction, Negishi coupling and olefin metathesis. One application of these methods is in the formation of nitrogen-containing heterocycles, an omnipresent feature of many biologically active alkaloids and synthetic drugs. The goal of this dissertation is to expand the known applications of sequential transition metal catalysis to the synthesis of highly substituted bridged *N*-heterocycles and their subsequent diversification. Our future goal is to have the methodologies described herein applied to combinatorial library synthesis.

The first project outlines a successful development of a new sequential transition metal-catalyzed methodology utilizing a copper-catalyzed three-component coupling followed by a palladium-catalyzed Heck cascade to form an aryl-fused isoquinuclidine (2-azabicyclo[2.2.2]octane) core. Diversification of the bridged core is then explored including palladium-catalyzed allylic functionalization and ruthenium-catalyzed cross-metathesis.

The second project described herein involves a sequential copper-catalyzed three-component coupling followed by a radical initiated intramolecular cyclization. By this process, diversification of the isoquinuclidine (2-azabicyclo[2.2.2]octane) core is achieved in the initial Cu-catalyzed reaction.

The third project describes our preliminary efforts at developing a sequential transition metal-catalyzed method for the preparation of a bicyclobenzazepine (1-azabicyclo[3.2.2]nonane) scaffold and the challenges faced there in.



*To my wife, Kristen, I couldn't have done it without you. I love you very much.....*

*.....and to Olivia, never stop learning*

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# Synthesis and Diversification of Bridged *N*-Heterocycles via Sequential Transition Metal-Catalyzed Reactions

<b><u>TABLE OF CONTENTS</u></b>	<b>Page #</b>
Abstract.....	iii
Acknowledgements.....	vi
Table of Contents.....	vii
Abbreviations.....	x
 <b>Chapter One: Prologue</b> .....	 1
<b>Chapter Two: Introduction</b> .....	4
<b>Part I: Bridged <i>N</i>-Heterocycles: Biological Activity and Preparation</b>	
2.1 Isoquinuclidines.....	6
2.1.1 Naturally Occurring Alkaloids.....	6
2.1.2 Synthetic Analogues.....	9
2.2 Bicycloazepines.....	19
2.2.1 Naturally Occurring Alkaloids.....	19
2.2.2 Synthetic Analogues.....	20
<b>Part II: Synthetic Methods</b>	
2.3 Pd-Catalyzed Heck Reaction.....	24
2.4 Radical Cascade Reaction.....	37
2.5 Cu-Catalyzed Three-Component Coupling Reaction.....	40
2.6 Ru-Catalyzed Olefin Metathesis.....	44
2.7 Functionalization of Allylic C-H Bonds.....	52
2.8 Hydroboration Reaction.....	60
2.9 Nucleophilic Substitution Reaction.....	61
 <b>Chapter Three: Synthesis and Diversification of Aryl-Fused</b>	
Azabicyclo[2.2.2]octanes via Cu/Pd/Ru Sequential Catalysis.....	63

<b>3.1 Cu-Catalyzed Three-Component Coupling</b> .....	65
<b>3.1.1 Optimization of Conditions</b> .....	65
<b>3.1.2 Variation of Aryl Imine</b> .....	67
<b>3.1.3 Variation of Vinyl Tin</b> .....	69
<b>3.1.4 Variation of Acid Chloride</b> .....	70
<b>3.2 Pd-Catalyzed Heck Cascade</b> .....	70
<b>3.2.1 Stereo- and Regioselectivity, Mechanism</b> .....	71
<b>3.2.2 Proof of Concept</b> .....	74
<b>3.2.3 Formation of Regioisomers</b> .....	76
<b>3.2.4 Synthesis of Analogues</b> .....	78
<b>3.3 Reactions with the Bridgehead Olefin in the Regioisomer Mixture</b> .....	81
<b>3.3.1 Acetoxylation</b> .....	81
<b>3.3.2 Tsuji-Trost and Organocuprate Substitution</b> .....	86
<b>3.3.3 Selenium Dioxide Oxidation</b> .....	87
<b>3.3.4 Allylic Bromination</b> .....	87
<b>3.3.5 Ireland-Claisen Rearrangement</b> .....	88
<b>3.3.6 Catalytic Hydrogenation</b> .....	89
<b>3.3.7 Acid-Catalyzed Isomerization</b> .....	91
<b>3.4 Return to Pd-Catalyzed Heck Cascade</b> .....	92
<b>3.4.1 Trapping Reactions</b> .....	92
<b>3.4.2 Heck Conditions for Single Isomer Formation</b> .....	95
<b>3.5 Reactions with the Bridgehead Olefin in the Single Regioisomer</b> .....	96
<b>3.5.1 Hydroboration</b> .....	96
<b>3.5.2 Cross Metathesis</b> .....	97
<b>3.6 Nucleophilic Substitution</b> .....	98
<b>Chapter Four: Synthesis of Functionalized Aryl-Fused Azabicyclo[2.2.2]octanes</b>	
<b>via Radical Cyclization</b> .....	101
<b>4.1 Method Development, Mechanism</b> .....	103
<b>4.2 Cu-Catalyzed Three-Component Coupling</b> .....	106
<b>4.3 Radical Cascade</b> .....	108
<b>4.3.1 Optimization of Conditions</b> .....	108

<b>4.3.2</b> <i>Synthesis of Analogues</i> .....	109
<b>Chapter Five:</b> <i>Attempts at Developing a Sequential Ru/Pd Protocol for the Synthesis of Bridged N-Heterocycles</i> .....	114
<b>5.1</b> <i>Cu-Catalyzed Three-Component Coupling</i> .....	115
<b>5.2</b> <i>Sequential RCM/Heck Annulations</i> .....	117
<b>Chapter Six:</b> <i>Experimental</i> .....	120
<b>Bibliography</b> .....	169
<b>Appendix:</b> <i>Selected NMR Spectra, GC-MS data and X-Ray Crystallographic Data</i> .....	187

## Abbreviations

Å	angstrom
μwave	microwave radiation
μL	microliter(s)
3CC	three-component coupling
9-BBN	9-borabicyclo(3.3.1)nonane
Ac	acetyl
ACN	acetonitrile
AIBN	azobisisobutyronitrile
Ar	aryl
Atm	atmosphere(s)
(S)-BINAP	(S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Bu	butyl
BQ	benzoquinone
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
cat.	Catalyst
Cbz	carboxybenzyl
CM	cross metathesis
Cy	cyclohexyl
d	day(s)
dba	dibenzylideneacetone

DCC	<i>N,N</i> -dicyclohexylcarbodiimide
DCM	dichloromethane
DIPEA	<i>N,N</i> -diisopropylethylamine
DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DMSO- $d_6$	dimethyl sulfoxide (deuterated)
dppe	1,2-bis(diphenylphosphino)ethane
E	electron withdrawing group
ee	enantiomeric excess
EI	electron impact
equiv.	equivalent(s)
Et	ethyl
<i>et al.</i>	and others
FAB	fast atom bombardment
g	gram(s)
GC-MS	gas chromatography - mass spectrometry
h	hour(s)
HRMS	high resolution mass spectrometry
IR	infrared spectrometry
KHMDS	potassium bis(trimethylsilyl)amide
LG	leaving group
L	ligand

Me	methyl
M	moles per liter
MHz	megahertz
min	minutes
mg	milligram(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
MS	4 Å molecular sieve
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NR	no reaction
Nu	nucleophile
Pdt	product
PG	protecting group
Ph	phenyl
PMB	<i>p</i> -methoxybenzyl
PNB	<i>p</i> -nitrobenzyl
ppm	parts per million
<i>i</i> -Pr	<i>iso</i> -propyl



R <sub>f</sub>	retention factor
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminumhydride
SM	starting material
rt	room temperature
TBAB	tetra- <i>n</i> -butylammonium bromide
TBAC	tetra- <i>n</i> -butylammonium chloride
TBDMS	<i>tert</i> -butyldimethylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TES	triethylsilane
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl
TosMIC	toluenesulfonylmethyl isocyanide
Ts	<i>para</i> -toluenesulfonyl

## **Chapter One**

### *Prologue*

Carbon-carbon bond forming reactions are an important area of modern synthetic organic chemistry. Classic reactions, including the Grignard reaction, Diels-Alder cycloaddition and many more, are widely applied in the synthesis of organic compounds. However, over the past 40 years a new approach to carbon-carbon bond formation has emerged. Transition metal catalysis is a powerful method of facilitating multiple transformations with high chemo-, regio-, and stereoselectivity, typically under mild conditions. Additionally, sequencing these methods together has allowed researchers to rapidly access organic compounds of ever increasing molecular complexity. Major advantages to sequential transition metal catalysis include avoidance of protection/deprotection chemistry and broad substituent tolerance, making these methods well suited for application to combinatorial library synthesis.

Our interest lies in the sequencing of these reactions in such a way to achieve the formation and subsequent diversification of bridged *N*-heterocycles. Ubiquitous in nature, nitrogen-containing compounds, and synthetic methods for accessing them, have become one of the central themes in modern synthetic organic chemistry. The goal of this dissertation is to expand our understanding of not only transition metal catalysis, but also the challenge of synthesizing and diversifying complex, structurally rigid, bridged scaffolds.

What follows is a brief description of the layout and content of this dissertation. Part I of chapter two outlines the biological activity and formation of two specific bridged *N*-heterocyclic scaffolds, including both naturally occurring alkaloids and synthetic privileged structures. Part II of chapter two discusses all the synthetic methods employed throughout the completion of this research project.

The next three chapters describe all of the experimental work conducted during this graduate project. Chapter three discusses our construction of the aryl-fused Isoquinuclidine (2-

azabicyclo[2.2.2]octane) ring system, using an intramolecular Heck cascade reaction. This is followed by an in-depth discussion of our efforts to diversify that core structure and our eventual success in attaching a second privileged structure via a flexible linker.

Chapter four explores the possibility of forming an analogous Isoquinuclidine (2-azabicyclo[2.2.2]octane) ring system, via an intramolecular radical cascade method. Proof of concept results have been acquired.

Chapter five outlines our initial attempts at obtaining an alternative bicyclobenzazepine (1-azabicyclo[3.2.X]octane) ring system via a reversed reaction order of Ru-catalyzed RCM followed by Pd-Catalyzed Heck (as compared to project 1)

## **Chapter Two**

### *Introduction*

## **Part I**

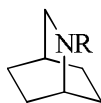
### *Bridged N-Heterocycles: Biological Activity and Preparation*

## 2.1 Isoquinuclidines

Bridged *N*-heterocycles can be found as the core structure in many naturally occurring alkaloids and synthetic privileged structures. For this reason, extensive research has gone into isolation and characterization of these alkaloids, development of total synthesis strategies, preparation of synthetic analogs, and exploration of their potential biological activity.

### 2.1.1 Naturally Occurring Alkaloids

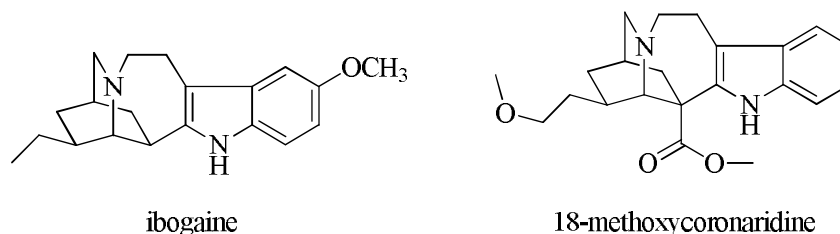
The isoquinuclidine (2-azabicyclo[2.2.2]octane) ring system, containing a non-bridgehead nitrogen, is a rigid scaffold present in a diverse range of biologically active alkaloids and synthetic privileged structures (Figure 2.1).



**Figure 2.1** 2-azabicyclo[2.2.2]octane ring system

Of these naturally occurring compounds, the Iboga family of alkaloids, primarily isolated for the *Tabernanthe* or *Tabernaemontana* species of plants, is by far the most studied (Figure 2.2).<sup>1</sup> Ibogaine was the first member of this vast family isolated and identified and has since been found active in the treatment of addiction including reduction of drug cravings and withdrawal symptoms.<sup>2</sup> However, ibogaine also possesses adverse tremorigenic, hallucinogenic, neurotoxic, and cardiovascular side effects leading investigators to search for safer and more effective structural derivatives.<sup>3</sup> One promising analogue is 18-methoxycoronaridine, which has been shown to retain the anti-addiction properties, without expressing the negative side effects, presumably due to an increased selectivity (Figure 2.2).<sup>3-4</sup> 18-methoxycoronaridine and its congeners have also shown promising reactivity in treatment of morphine, cocaine, alcohol, methamphetamine and nicotine addiction in rats.<sup>5</sup> In addition, iboga-type indole alkaloids have

demonstrated promising pharmacology including anti-diarrheal activity,<sup>6</sup> antifungal, anti-HIV, anti-cholinesterasic and leishmanicide activities.<sup>1a</sup>

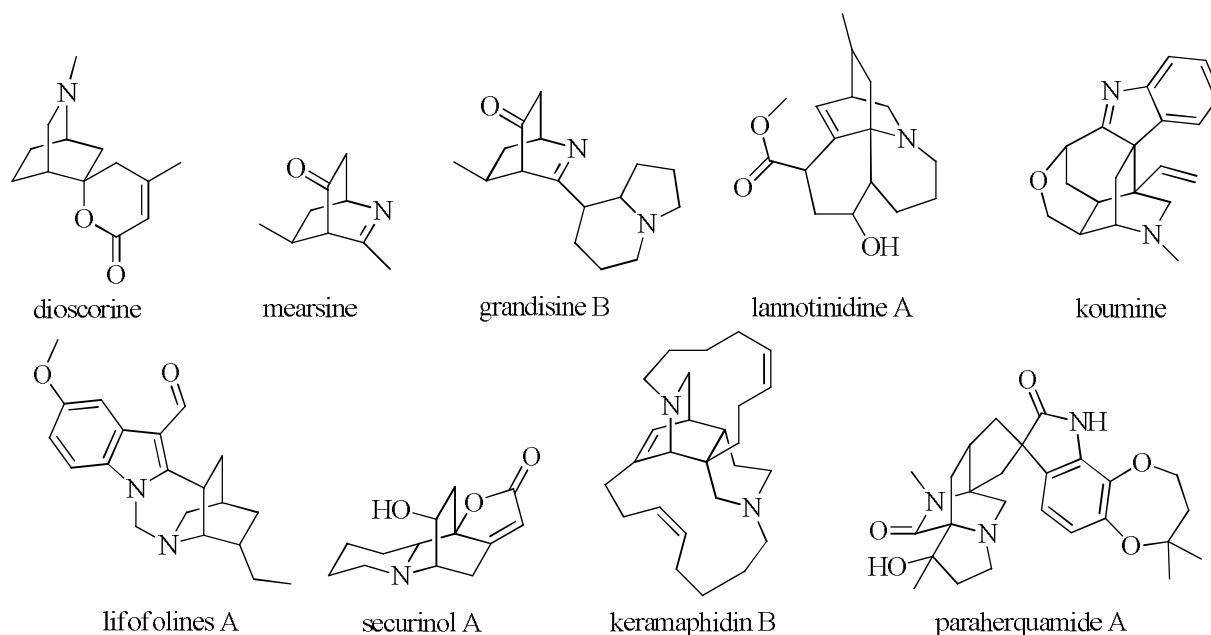


**Figure 2.2** Representative *iboga alkaloids*

What follows is a brief summary of the structures and activities of other alkaloids (Figure 2.3). Dioscorine is a toxic central nervous system depressant and modulator of the nicotinic acetylcholine receptor.<sup>7</sup> Mearsine<sup>8</sup> and grandisine B<sup>9</sup> are two rare isoquinuclidinone alkaloids containing the unusual azabicyclo[2.2.2]oct-2-en-5-one core. Grandisine B, a structurally novel indolizidine alkaloid, from the Australian rainforest tree *Elaeocarpus grandis*, has demonstrated binding affinity for the human  $\delta$ -opioid receptor.<sup>9</sup> Lannotinidines A, a member of the *Lycopodium* family of alkaloids, was recently isolated and shown to enhance mRNA expression for nerve growth factor.<sup>10</sup> Koumine, an alkaloid of *Gelsemium elegans* (Benth.), has shown analgesic effects in rodents for inflammatory and neuropathic pain.<sup>11</sup> Lirofoline A, another alkaloid isolated from the genus *Tabernaemontana*, has shown major activity in reversing multidrug resistance in vincristine-resistant KB cells.<sup>12</sup> Securinega alkaloids (including securinol A), isolated from the plant family *Euphorbiaceae*, has an intriguing bridged tetracyclic structure and wide ranging biological activity. In addition to use in traditional Chinese medicine, securinega alkaloids have been investigated for their cytotoxicity in the treatment of Bell's palsy, ALS symptoms, aplastic anemia, malaria, bacterial infection and leukemia.<sup>13</sup> Keramaphidin B, a member of the manzamine family of alkaloids and believed to be a plausible biogenetic precursor of ircinal A (not shown), has shown anticancer activity in the treatment of leukemia

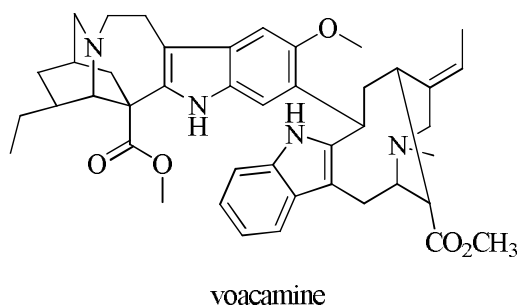


and human epidermoid carcinoma.<sup>14</sup> Paraherquamide A is a secondary metabolite, with potent antiparasitic and antinematodal activity.



**Figure 2.3** Alkaloids containing an isoquinuclidine core

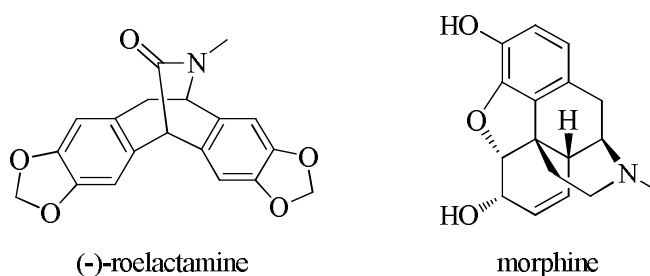
Bisindole alkaloids are a class of molecules consisting of two indole moieties joined by a flexible alkyl linker. One prominent example of a naturally occurring bisindole alkaloid, containing the isoquinuclidine ring system, is the vobasiny-iboga family of alkaloids (Figure 2.4, voacamine shown). Vobasiny-iboga bisindole alkaloids have demonstrated activity in the treatment of Alzheimer's disease,<sup>15</sup> plasmodia,<sup>16</sup> leukemia and lung cancer tumors,<sup>17</sup> other forms of cancer<sup>18</sup> and more.<sup>19</sup>



**Figure 2.4** Bisindole alkaloid voacamine

Due to the previously mentioned biological activity of naturally occurring alkaloids, containing the isoquinuclidine core, there has been extensive interest in developing efficient total synthesis strategies.<sup>1a, 13, 20</sup>

Observing the previously summarized alkaloids it should be noted that aryl-fused isoquinuclidines have, thus far, not been found in nature. Similar scaffolds, containing an aryl-fused *N*-heterocycle as part of a different core structure, include roelactamine<sup>21</sup> (active against Parkinson's and Alzheimer's disease) and morphine<sup>22</sup> (opiate analgesic) (Figure 2.5).



**Figure 2.5** Alkaloids containing a similar bridged *N*-heterocyclic core

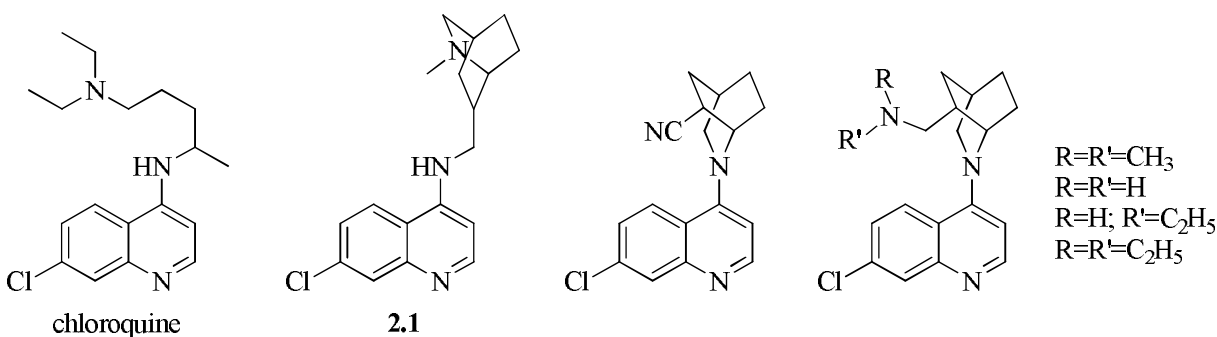
### 2.1.2 Synthetic Analogues

In addition to the previously mentioned naturally occurring alkaloids, a vast array of isoquinuclidine containing privileged structures have been prepared over the years and tested for their potential biological activity. What follows is a summary of the diverse pharmacological effects of these synthetic agents, including several dimeric scaffolds which have been tethered together to explore new avenues of biological activity.<sup>23</sup>

A common feature in many of the biologically active substances outlined below is the use of an isoquinuclidine ring system to establish a “conformationally rigid” framework. Analogues of flexible compounds which have demonstrated potent biological activity are synthesized containing the rigid bridge skeleton, thereby forcing them into a more reactive conformation. An

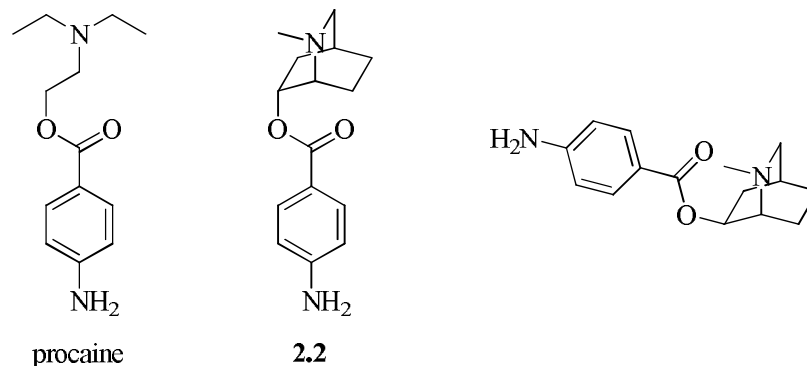
analogous scenario is in the Diels-Alder cycloaddition reaction, where dienes that are forced into the *s*-cis conformation are more reactive than flexible dienes.

Effects on the conformational reactivity of a previously identified biologically active compound were explored in a recent publication by Borne *et al.* who synthesized a series of isoquinuclidine analogs of chloroquine (Figure 2.6).<sup>24</sup> Chloroquine is a widely used antimalarial agent which has unfortunately become less effective due to drug resistance.<sup>25</sup> All six analogues showed *in-vitro* antimalarial and antileishmanial activity, with compound **2.1** being the most potent in both cases (two times more than chloroquine). Although the specific mode of activity is still not known, the semirigid nature of these molecules is believed to be a contributing factor.



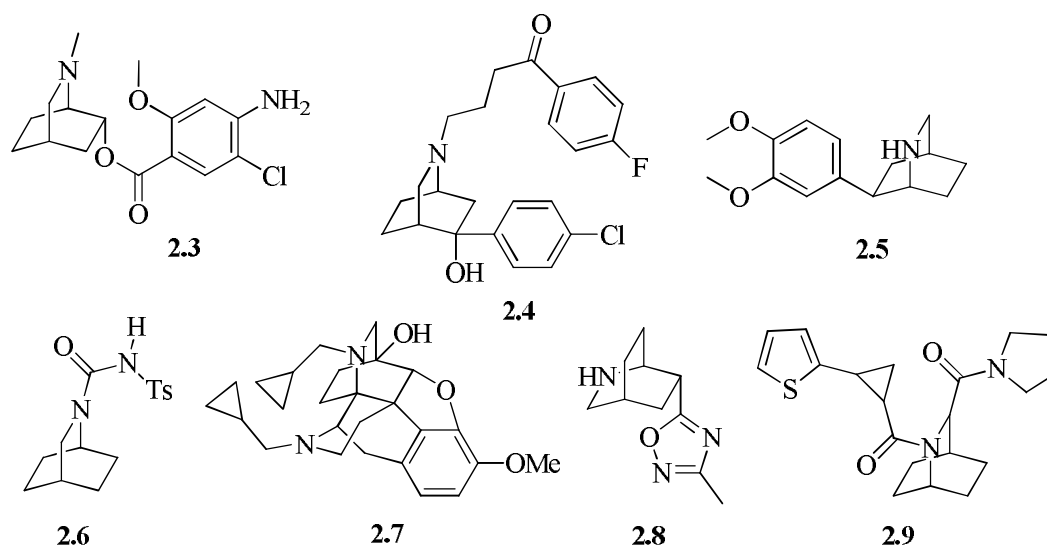
**Figure 2.6** Chloroquine and isoquinuclidine containing analogues

This relationship between rigidity and activity was also demonstrated by Iriepa *et al.* who synthesized several isoquinuclidine containing analogues of procaine to investigate their anesthetic activity.<sup>26</sup> A range of activity was revealed including ester linkages being more reactive than amides and *anti* stereoisomers more reactive than *syn*. Compound **2.2** proved to be the most potent with a threefold improvement in activity and duration of action when compared to local anesthetic procaine.



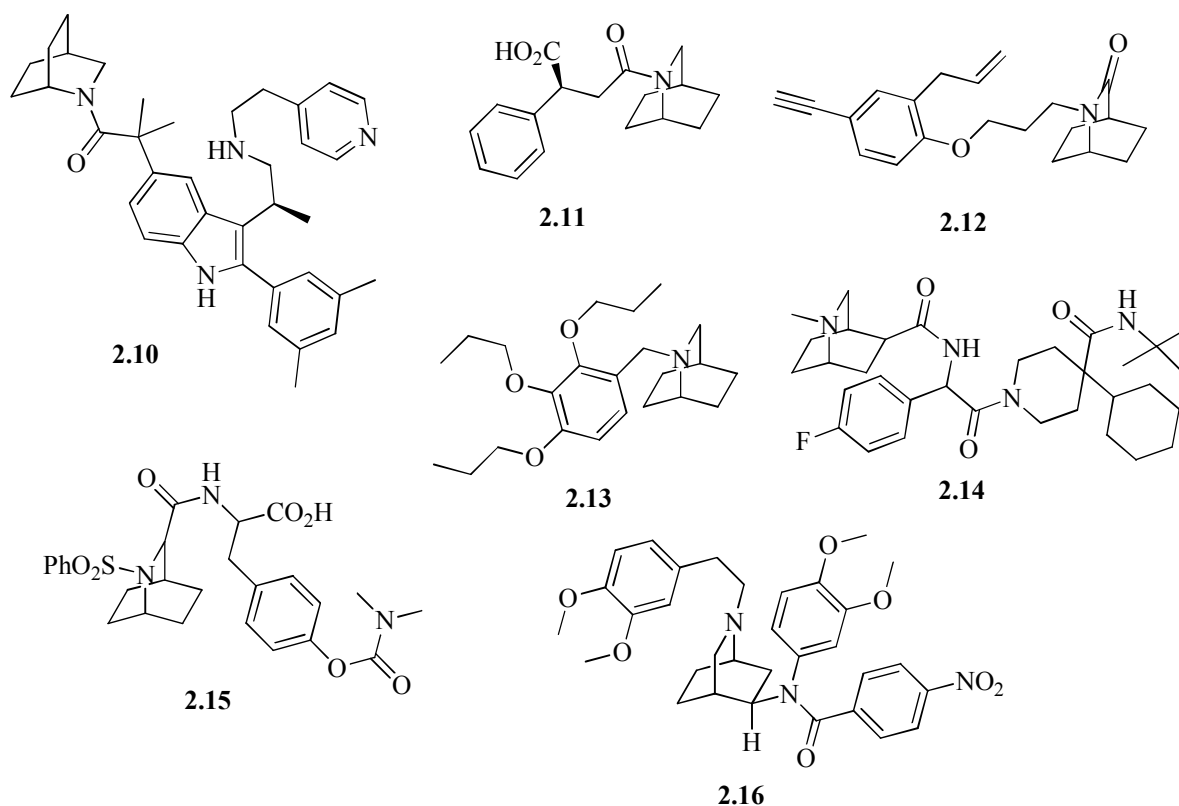
**Figure 2.7** Procaine and isoquinuclidine containing analogues

An important subclass of pharmaceutical isoquinuclidines is central nervous system active agents (Figure 2.8). Iriepa *et al.* synthesized a family of compounds possessing an isoquinuclidine tethered to 4-amino-5-chloro-2-methoxybenzoate and identified promising reactivity from analogue **2.3** for the treatment of nausea and vomiting (5-HT<sub>3</sub> antagonists).<sup>26</sup> A common feature, characteristic of nearly all potent 5-HT<sub>3</sub> antagonists, is an aromatic ring at a specified distance from a carbonyl and a basic site.<sup>26-27</sup> Additional examples include antipsychotic **2.4**,<sup>28</sup> psychotomimetic agent **2.5**,<sup>29</sup> sedative **2.6**<sup>29</sup> and analgesic **2.7**,<sup>30</sup> as well as others active against Alzheimer's disease related learning and memory issues (**2.8**)<sup>31</sup> and dementia related memory loss (**2.9**).<sup>32</sup>



**Figure 2.8** Isoquinuclidine containing privileged structures with central nervous system activity

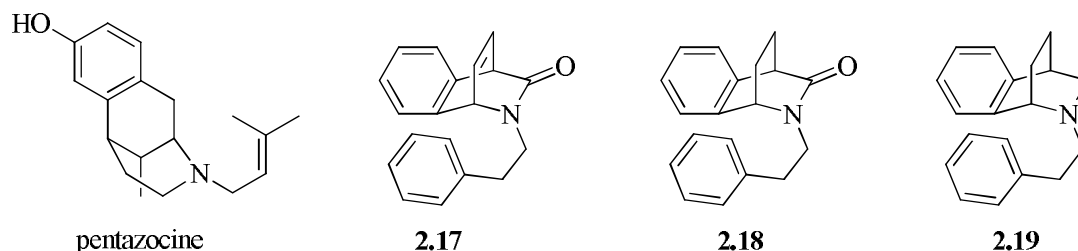
In addition to central nervous system active agents, privileged structures containing the isoquinuclidine scaffold has shown promising biological activity including: hormone suppression (**2.10**),<sup>33</sup> lowering blood sugar (**2.11**),<sup>29</sup> cholesterol biosynthesis suppression (**2.12**),<sup>29</sup> increased bronchial secretion (**2.13**),<sup>34</sup> treatment of obesity, diabetes and sexual dysfunction (**2.14**),<sup>35</sup> autoimmune and inflammatory disease treatment (**2.15**)<sup>36</sup> and suppression of abnormal heart rhythms (**2.16**)<sup>37</sup> (Figure 2.9).



**Figure 2.9** Biologically active privileged structures with an isoquinuclidine core

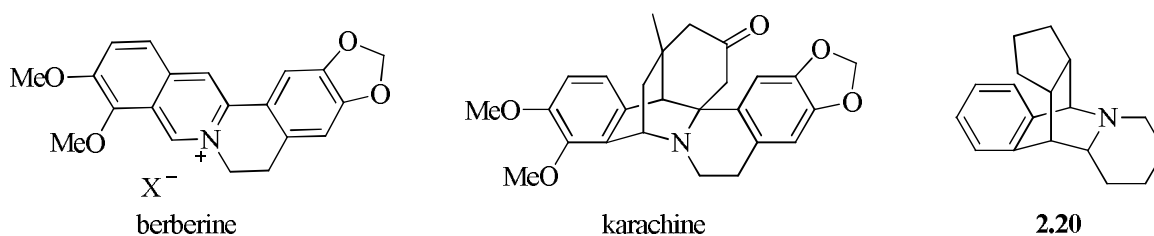
Looking at the previously described synthetic agents, we once again see a lack of aryl-fused analogues. However, an exhaustive search of the literature did reveal a limited number of examples.<sup>38</sup> Isoquinuclidine containing analogues of pentazocine, a synthetic opioid analgesic, were prepared (**2.17-2.19**) and tested for possible analgesic and central nervous system activity

(Figure 2.10).<sup>39</sup> Although all three analogues failed to express analgesic activity at the doses tested, lactam analogues **2.17** and **2.18** did show promising central nervous system activity.



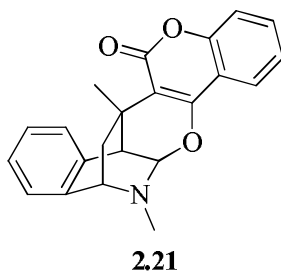
**Figure 2.10** *Pentazocine and isoquinuclidine containing analogues*

Karachine, an unusual protoberberine alkaloid, was isolated and fully characterized in the early 1980's, revealing that the compound was not a natural product but rather the result of berberine and two molecules of acetone reacting during isolation (Figure 2.11).<sup>40</sup> Although karachine itself has not yet been screened for potential biological activity, other protoberberine alkaloids have demonstrated antimicrobial, anti-inflammatory and antimalarial activity (among others).<sup>41</sup> Analogous isoquinuclidine containing scaffold **2.20** has also been prepared and shown to be a potent noncompetitive *N*-methyl-*D*-aspartate antagonist (anesthetic).<sup>42</sup>



**Figure 2.11** *Protoberberine alkaloids and an isoquinuclidine containing synthetic analogue*

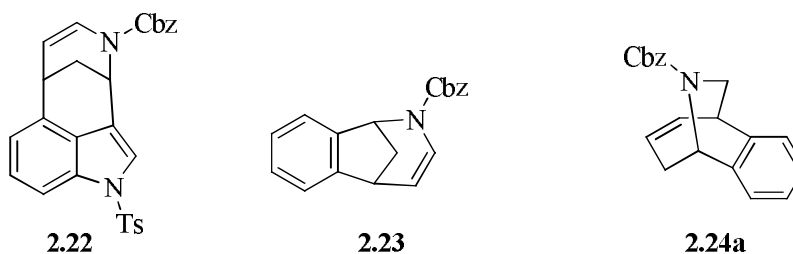
One final example of an aryl-fused isoquinuclidine compound, which has recently been published, is oxazatricycle **2.21** (Figure 2.12).<sup>43</sup> Although biological activity screening was not conducted, analogues of the oxazatricycle structure did demonstrate interesting molecular switching properties.



**Figure 2.12** *Isoquinuclidine containing oxazatricycle*

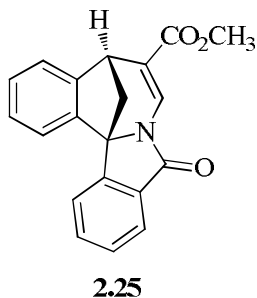
The observed lack of biological activity studies and preparation strategies pertaining to isoquinuclidine containing alkaloids and synthetic agents represents a significant gap in the literature, towards which I have focused the majority of my graduate research.

Analogous aryl-fused *N*-heterocycles, possessing a different core structure, have been synthesized by Martin *et al.* Using sequential transition-metal catalysis, they have been able to synthesize a series of natural product analogues including benzomorphans **2.22** and **2.23** (similar to morphine) and bicyclobenzazepine **2.24a** (similar to roelactamine).<sup>44</sup> Biological screening is currently in progress; however preliminary studies indicate promising activity in the treatment of Alzheimer's disease and cancer.<sup>45</sup>



**Figure 2.13** *Aryl-fused bridge N-heterocyclic analogues of morphine and roelactamine*

Bridged *N*-heterocyclic scaffold **2.25** has recently been constructed by Kim *et al.* using a Heck cascade type reaction, however biological screening is yet to be undertaken (Figure 2.14).

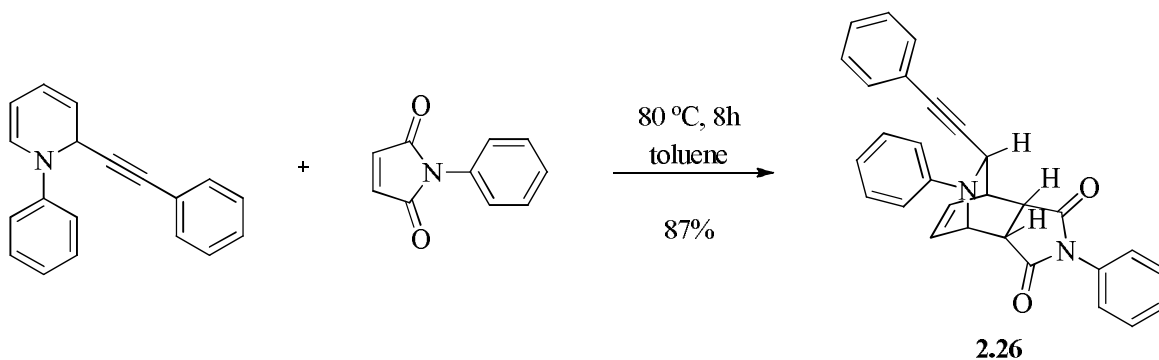


**Figure 2.14** *Aryl-fused bridge N-heterocycle*

### Preparation of Synthetic Analogues

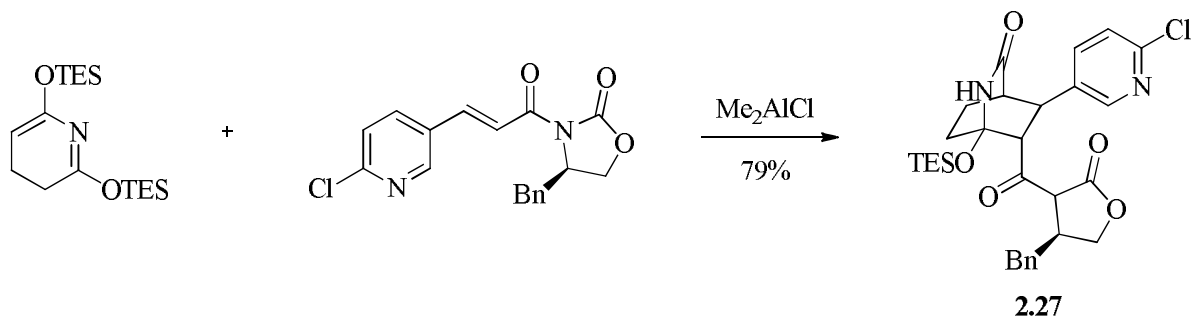
Due to the demonstrated vast abundance of biologically active alkaloids and privileged structures which contain the isoquinuclidine core, a wide range of methods have been applied to the construction of this unique structural motif.<sup>29</sup> Of these methods, the Diels-Alder reaction, including asymmetric synthesis, is by far the most commonly employed.<sup>46</sup> Use of a Diels-Alder cycloaddition reaction was recently demonstrated via cyclization of 1,2-dihydropyridine with *N*-phenyl maleimide to form bridged product **2.26** in an 87% yield as a single diastereomer (Scheme 2.1).<sup>47</sup> A similar asymmetric hetero Diels-Alder reaction was implemented by Evans *et al.* in their total synthesis of (-)-epibatidine (not shown); affording bridged product **2.27** (Scheme 2.2).<sup>48</sup> A 79% yield of the *exo* diastereomer was obtained.

#### Scheme 2.1



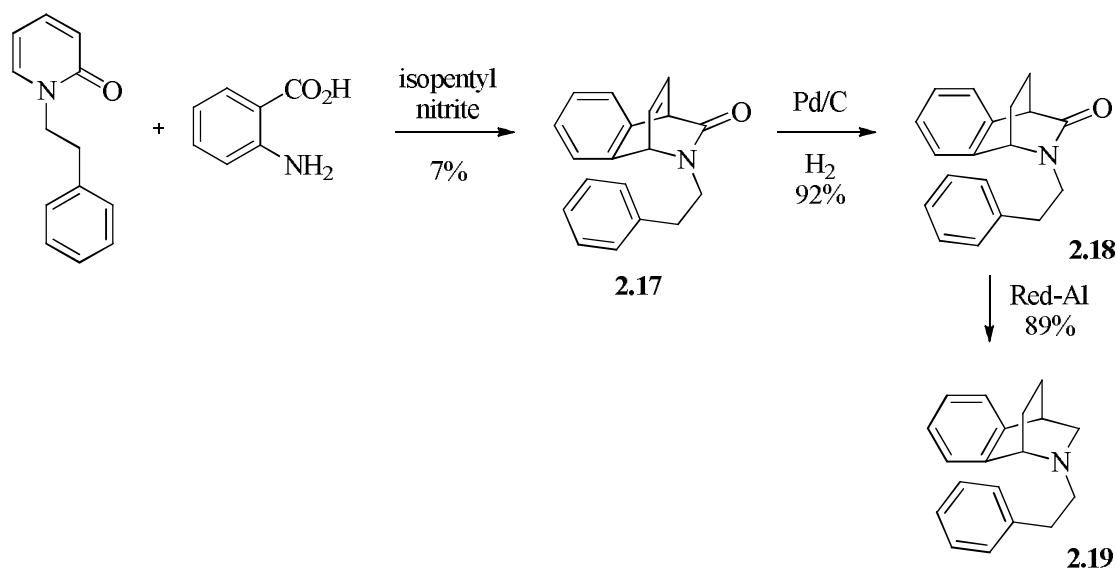


## Scheme 2.2



A third example, implemented by Borne *et al.*, employs a benzyne Diels-Alder to obtain aryl-fused bridged lactam **2.17**, in an unfortunately low 7% yield (Scheme 2.3).<sup>39, 49</sup> Subsequent catalytic hydrogenation and reduction yielded **2.18** and **2.19** respectively, both in good yields. In spite of the low 7% yield, this method represents one of only a limited number of methods capable of forming the aryl-fused isoquinuclidine core.<sup>38</sup> The Diels-Alder method is also limited due to the sensitive electronic requirements of the aryl component.

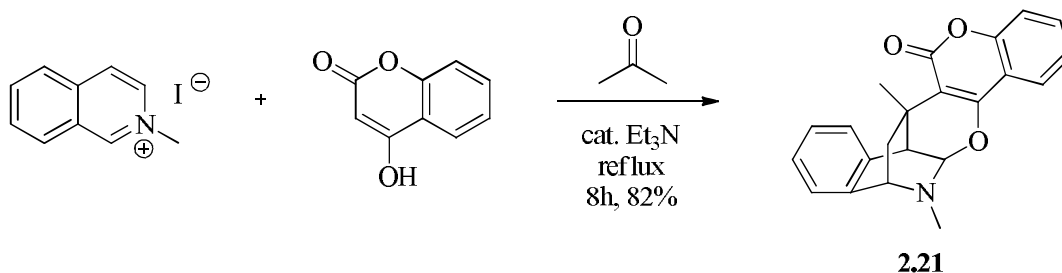
## Scheme 2.3



To date, there has only been one combinatorial library synthesis method of constructing the isoquinuclidine core published. Yang *et al.* developed a cycloaddition protocol for forming

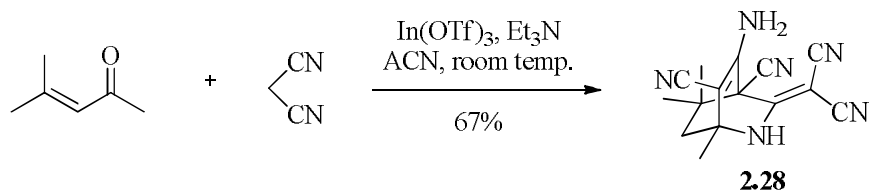
oxazatricycles via parallel solution-phase synthesis. Nine analogues were synthesized in yields ranging from 62 to 93%, including oxazatricycle **2.21** at 82% (Scheme 2.4).<sup>43</sup> This method, in addition to the benzyne Diels-Alder reaction, constitutes the only strategy identified thus far for obtaining the aryl-fused isoquinuclidine core.

**Scheme 2.4**



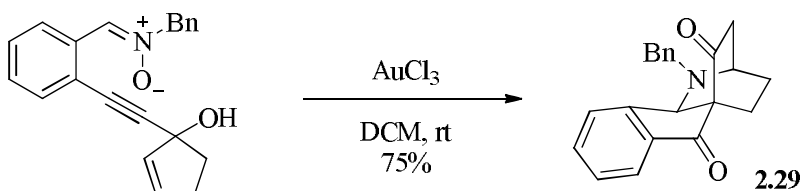
Efficient one-pot synthesis of an isoquinuclidine scaffold was accomplished via a novel cascade presumed to involve an aldol-type condensation, Michael addition, addition to a nitrile group and finally an annulation to afford azabicyclooctane **2.28** in a 67% yield (Scheme 2.6).<sup>50</sup>

**Scheme 2.5**



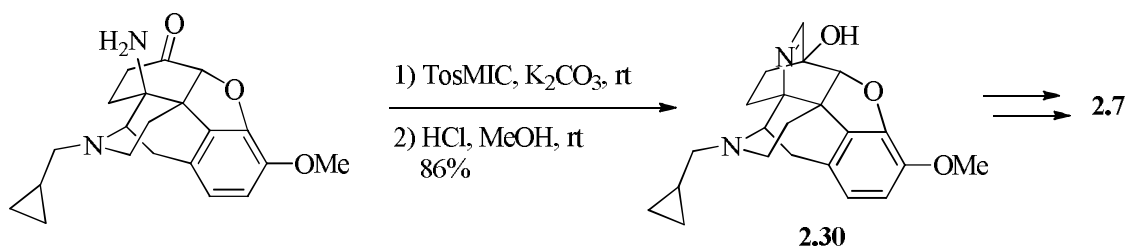
Another recent method, employed by Shin and *et al.*, utilized a gold-catalyzed redox-pinacol-Mannich-Michael cascade reaction to construct the isoquinuclidine core (**2.29**) in a 75% yield (Scheme 2.6).<sup>51</sup>

**Scheme 2.6**

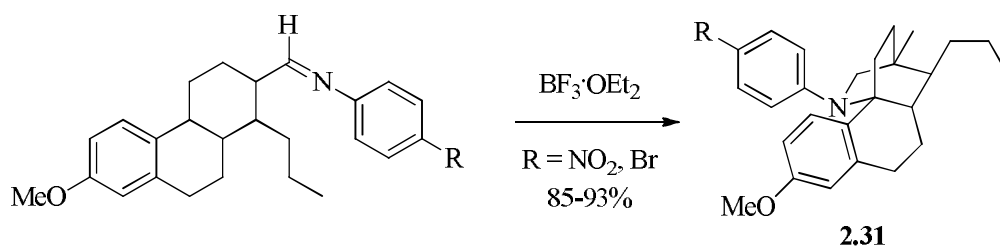


Other strategies recently employed include intramolecular condensation to afford imine **2.30** (Scheme 2.7),<sup>30</sup> domino 1,5-hydride shift formation of amide **2.31** (Scheme 2.8),<sup>52</sup> intramolecular nitron-olefin [3+2]-cycloaddition synthesis of bridged scaffold **2.32** (Scheme 2.9)<sup>53</sup> and a Mannich-aza-Michael cyclization to afford 16 compounds with amine **2.33** as a common core (Scheme 2.10).<sup>54</sup>

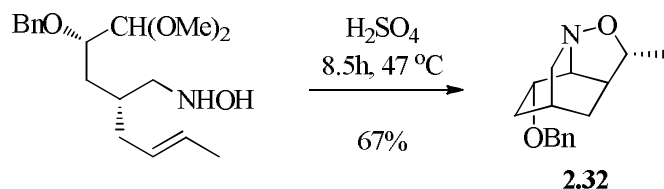
**Scheme 2.7**



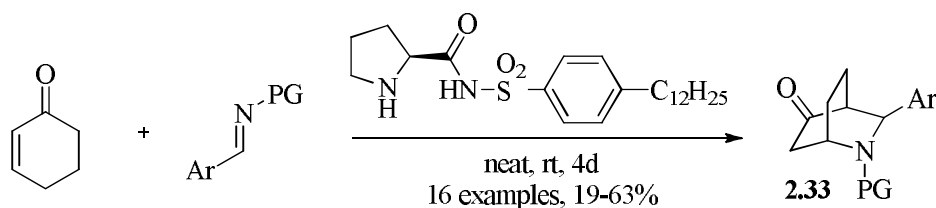
**Scheme 2.8**



**Scheme 2.9**

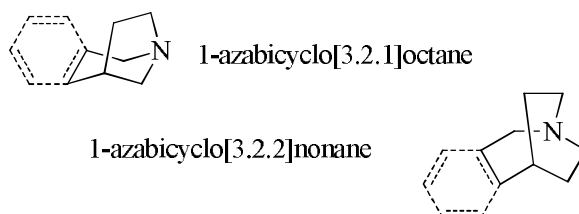


**Scheme 2.10**



## 2.2 Bicycloazepines

The bicyclobenzazepine and bicycloazepine (1-azabicyclo[3.2.x]octane) ring systems (with nitrogen at the bridgehead) are common rigid structural motifs found in various biologically active alkaloids and synthetic privileged structures (Figure 2.15). Whereas aryl-fused analogues of the isoquinuclidine core are rare, bicyclobenzazepines are relatively more common.

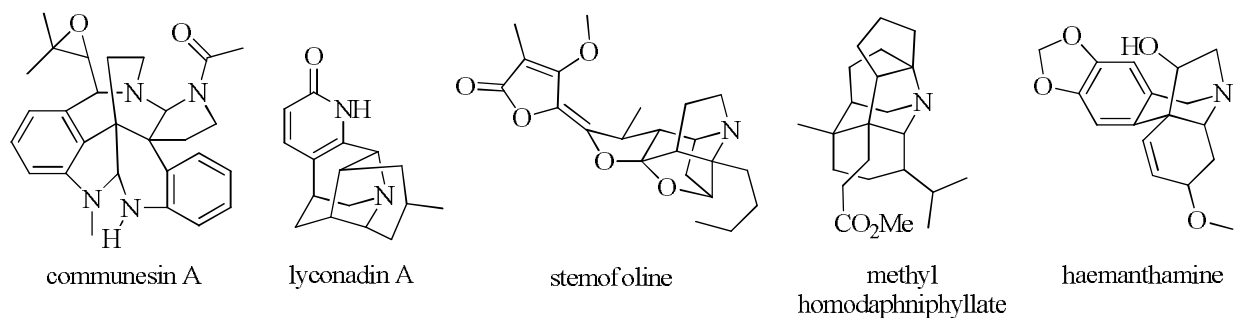


**Figure 2.15** 1-azabicyclo[3.2.X]octane) ring system ( $X = 1-2$ )

### 2.2.1 Naturally Occurring Alkaloids

Naturally occurring agents containing a bicycloazepine scaffold include communesins,<sup>55</sup> lyconadins,<sup>56</sup> stemofolines,<sup>57</sup> daphnanes and crinine (Figure 2.16). Communesins (communesin A shown) are a class of polycyclic indole alkaloids isolated from various species of marine fungus which exhibit antileukemic and insecticidal activities.<sup>55</sup> Lyconadins (lyconadine A shown) are a subclass of the lycopodium family of alkaloids which contains as many as 201 members. Lyconadin A was first isolated in 2001 and has since shown activity against lymphoma and human epidermoid carcinoma cells.<sup>56</sup> Stemofoline, from the stemona alkaloids, is a potent insecticide and acetylcholinesterase inhibitor (treats glaucoma, Alzheimer's disease and more).<sup>57</sup> The daphniphyllum alkaloids (including methyl homodaphniphyllate) are a vast collection of naturally occurring molecules with unusual and diverse ring systems. However, although select members exhibit mild cytotoxicity against lymphoma, adequate pharmacological activity studies have thus far not been undertaken.<sup>58</sup> Haemanthamine, from the *pancratium*

alkaloid family, possesses antioxidant and anticonvulsant activity.<sup>59</sup> Due to the complexity found in these unusual ring systems there has been great interest in total synthesis and biosynthetic studies of these challenging targets.<sup>55-57, 60</sup>

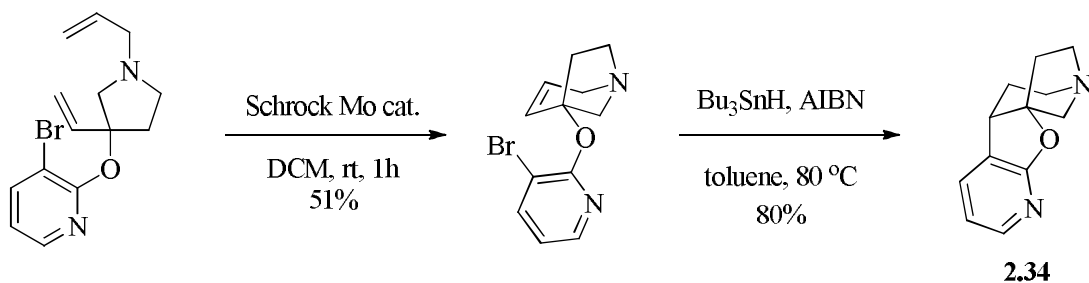


**Figure 2.16** Alkaloids with a bicycloazepine core

## 2.2.2 Synthetic Analogues

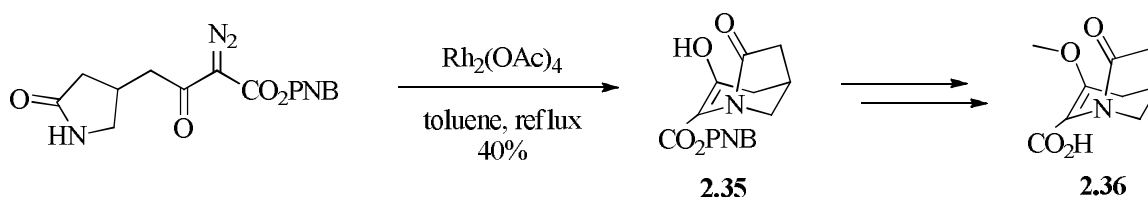
In addition to alkaloid total synthesis there has been an interest in formation and biological testing of synthetic targets (privileged structures) containing the bicycloazepine ring system. Chemists at the Eli Lilly & Co. pharmaceutical company have developed a method of synthesizing a series of pyridine fused polycyclic amines in order to investigate their selective activation or inhibition of biological receptors (Scheme 2.11).<sup>61</sup> Bicycloazepine **2.34** was constructed in two steps via sequential ring-closing metathesis followed by radical cyclization; however screening for possible biological activity has not yet been undertaken.

**Scheme 2.11**



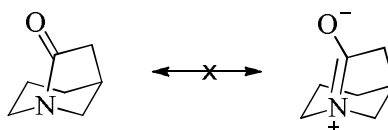
Another company, Aventis Pharma, published a novel protocol for the formation of bridged  $\gamma$ -lactams analogues of  $\beta$ -lactam antibiotics (Scheme 2.12).<sup>62</sup> Bicycloazepine formation was accomplished via a rhodium-catalyzed carbenoid cyclization reaction affording bridged *N*-heterocycle **2.35** in a modest 40% yield. Unfortunately, this product proved highly unstable resulting in degradation during silica gel chromatography; however, via protection/deprotection they were then able to obtain stable carboxylic acid derivative **2.36**. The carboxylic acid variant exhibited weak antibiotic activity, while the ester form showed none at the doses tested.

**Scheme 2.12**



The instability observed for bridged  $\gamma$ -lactam **2.35** highlights a common challenge in bicycloazepine synthesis. Bridged bicyclic lactams (bicycle caprolactams) which contain the amide nitrogen in the bridgehead position are known as twisted amides due to their inability to achieve resonance stabilization. This reduction in resonance conjugation is the result of partial or complete disconnection of the nitrogen lone pair and the carbonyl, causing the amide to behave more like an amino ketone (Scheme 2.13).<sup>63</sup>

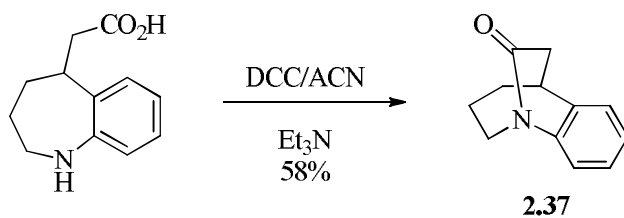
**Scheme 2.13**



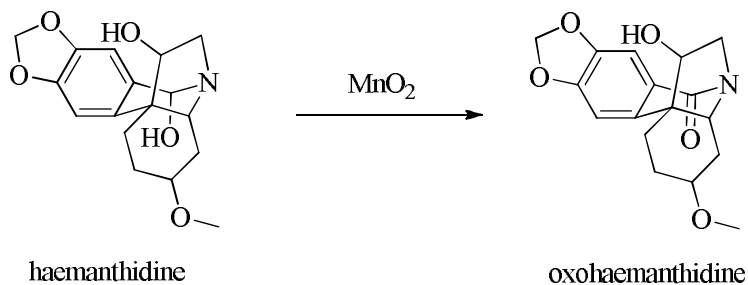
In spite of this challenging instability, a limited number of aryl-fused twisted lactams (bicyclocaprolactams) have been successfully synthesized. Brown *et al.* obtained twisted amide

**2.37**, via a condensation reaction, in a 58% yield (Scheme 2.14).<sup>64</sup> A second example is the  $\text{MnO}_2$  oxidation of haemanthidine to afford oxohaemanthidine (Scheme 2.15).<sup>65</sup>

**Scheme 2.14**



**Scheme 2.15**



## **Part II**

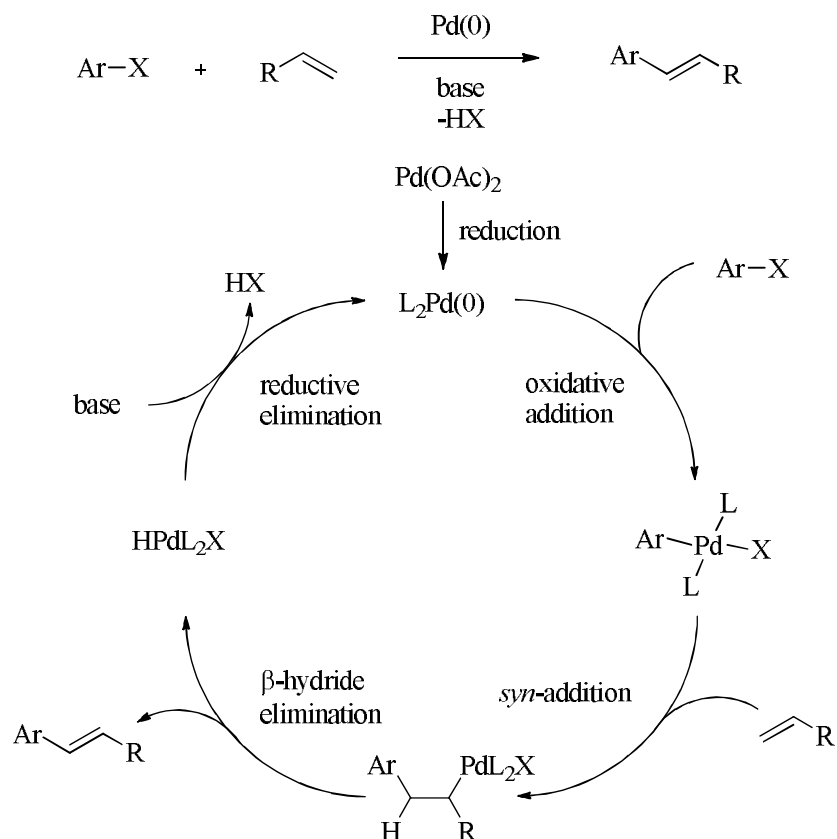
### *Synthetic Methods*



### 2.3 Pd-Catalyzed Heck Reaction

The Heck reaction, first described by Richard F. Heck, is one of the most powerful and versatile synthetic strategies used by organic chemists today. This reaction is a Palladium-mediated cross-coupling between an aryl (vinyl) halide and an alkene under basic conditions (Scheme 2.16). The mechanism begins with the Pd precatalyst (commonly  $\text{Pd}(\text{OAc})_2$ ) being reduced *in-situ* to form a reactive  $\text{Pd}(0)$  species, which then enters the catalytic cycle. Oxidative addition of the aryl halide to the  $\text{Pd}(0)$  complex is followed by *syn* addition to an olefin via carbopalladation. Next, the complex undergoes an internal C-C bond rotation to place a  $\text{sp}^3$ -bonded  $\beta$ -hydrogen in a *syn* alignment with the palladium atom. The complex then goes through a reversible  $\beta$ -hydride elimination to generate the desired substituted olefin. The final step is reductive elimination of the hydridopalladium(II) halide to regenerate the active  $\text{Pd}(0)$  complex, which helps to shift the equilibrium toward product.<sup>66</sup>

#### Scheme 2.16



The Heck reaction, which has been broadly applied in modern synthetic organic chemistry, possesses a seemingly endless combination of reaction conditions.<sup>66</sup> For the purposes of this text, important variables to consider include substrate, solvent, temperature, catalyst, ligand/ligandless, base and additive.

Considering substrate dependence, the Heck reaction typically requires an aryl, benzyl or vinyl halide (Br, Cl) although triflates are also frequently employed. Common catalysts include palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0) and palladium chloride. A wide variety of ancillary ligands can be used in the Heck reaction to stabilize the catalyst with the most common being  $\text{Ph}_3\text{P}$ . In addition to phosphine ligands, the Heck reaction can be improved (or hindered) by the presence of other chelating agents including bases, anions, olefins and the solvent. The base has four roles including: stabilization of the  $\text{Pd(0)}$  complex, reducing the rate of oxidative addition, speeding up the carbopalladation step and recycling the  $\text{Pd(0)}$  complex

thereby causing the  $\beta$ -hydride elimination equilibrium to favor products. Typical bases include  $\text{Et}_3\text{N}$  and  $(n\text{-Bu})_3\text{N}$  for nonpolar solvents and inorganic bases (acetates, carbonates, bicarbonates, phosphates and fluorides) for polar solvents. An example of a Heck reaction where an additive is used would be those developed by Jeffery *et al.* employing a quaternary ammonium salt (i.e. TBAC or TBAB).<sup>67</sup> Quaternary ammonium salts are useful in reactions where the addition of supporting ligands would crowd the palladium coordination sphere. A coordination sphere may become crowded when fragments of the substrate itself, including heteroaromatic rings, aminoacrylates and olefins, are capable of coordinating to the palladium catalyst. Use of Jeffery conditions also allows for lower reaction temperatures. The Heck reaction can generally be achieved in any solvent; however the majority of Heck reactions favor an aprotic, polar solvent, including Lewis basic organic solvents (DMF, DMA, or DMSO), aqueous solvents or ionic liquids. Ligand accelerated Heck reactions favor solvents of lower polarity such as toluene, dioxane and THF.

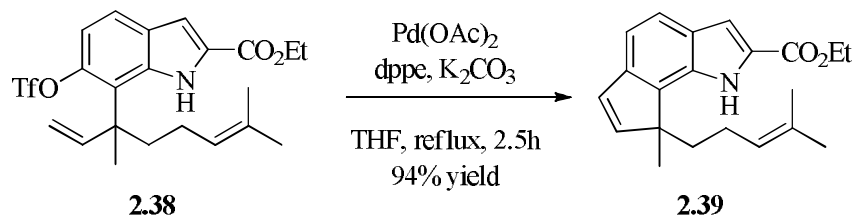
### **Intramolecular Heck/Carbocycle Formation**

An intramolecular Heck cyclization can be defined as coupling of a vinyl/aryl halide with a tethered alkene.<sup>68</sup> The intramolecular Heck reaction is capable of forming a wide range of ring sizes, ranging from 3 to over 14, with medium sized (5-7) ring formation being the most common. Furthermore, cyclization may occur through either an *exo* or *endo* fashion based on ring size as described by Baldwin rules.<sup>69</sup> Baldwin's rules are a qualitative set of generalizations establishing the probability (kinetic feasibility) of ring closure. When two inequivalent cyclization pathways exist, one is commonly favored (low energy, fast) and the other disfavored (high energy, slow). With Heck cyclizations this implies that carbopalladation will proceed through a trigonal system in either an *exo* or *endo* fashion. A favored cyclization is one that

allows the C-Pd to achieve a trajectory of approach to the olefin through low energy natural bond angles. Alternatively, a disfavored cyclization would require severe, high energy bond angles and/or distorted bond lengths. Select Baldwin's rules include: 3- to 7-*exo-trig* cyclizations favored, 3- to 5-*endo-trig* disfavored, and 6- to 7-*endo-trig* favored.<sup>69</sup>

For the purpose of this text, our primary interest is in the preference for a 5-*endo-trig* vs. a 6-*exo-trig* cyclization. Baldwin rules (and literature precedent)<sup>68</sup> suggest a 6-*exo-trig* cyclization should be favored over a 5-*endo-trig*, however it is important to realize that these are only general rules. Although rare, 5-*endo-trig* type products have been synthesized, however, their formation is typically explained via an alternative mechanism than direct cyclization and they are seldom competing against a possible 6-*exo-trig* pathway.<sup>70</sup> The first known example of a 5-*endo-trig* path being favored, in the presence of a competing 6-*exo-trig* cyclization, was recently published by Tanner *et al.* in 2006 (Scheme 2.17).<sup>71</sup> Aryl triflate **2.38**, cyclizing exclusively through a 5-*endo-trig* mechanism, afforded tricycle **2.39** in a 94% yield. The rationale for this unexpected outcome states that the steric bulk of the adjacent quaternary carbon is forcing the mono-substituted olefin into a close proximity with the aryl-palladium, forcing the 5-*endo-trig* cyclization event.<sup>71</sup>

**Scheme 2.17**

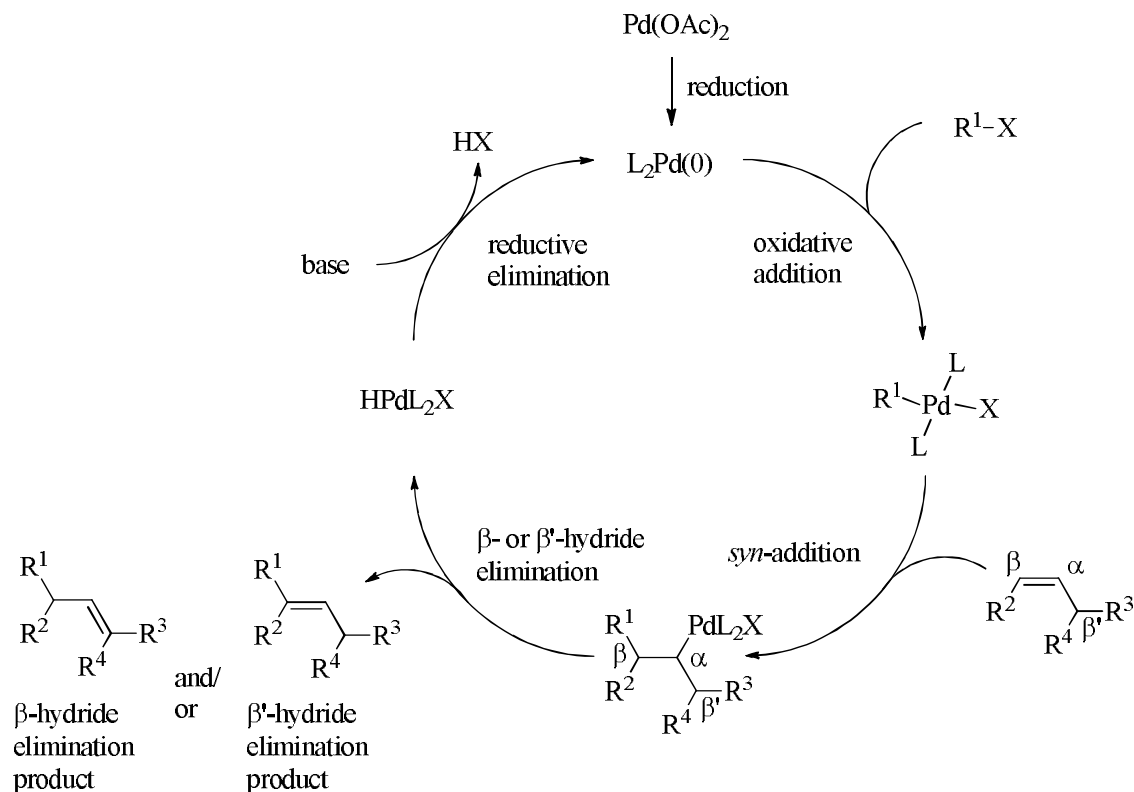


### Formation of Regioisomers

One major challenge of the Heck reaction is the potential for alkene isomerization, typically arising due to competing  $\beta$ - and  $\beta'$ -hydride elimination pathways (Scheme 2.18).<sup>72</sup>

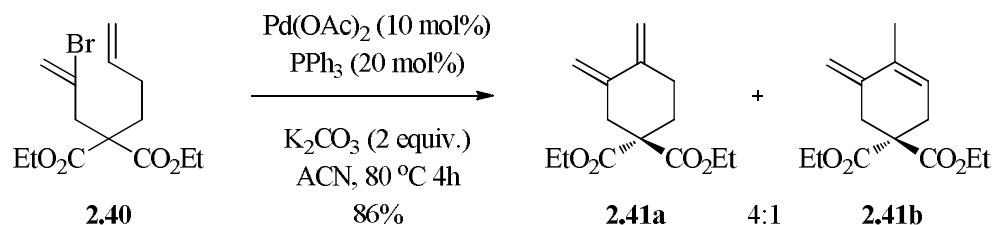
This problem can sometimes be avoided using alkenes with unsymmetric steric and electronic properties ( $\text{CH}_2=\text{CHCO}_2\text{R}$ ); however, the reversibility of  $\beta$ -hydride elimination can still be an issue.  $\beta$ -Hydride elimination reversal (readdition of the palladium hydride to the alkene) can be followed by an undesired alternative  $\beta'$ -hydride elimination.

**Scheme 2.18**



An example of this regioisomer formation issue was outlined in 1984 by Grigg *et al.* (Scheme 2.19).<sup>72c</sup> Heck cyclization of vinyl bromide **2.40** proceeded in a *6-exo-trig* fashion, to afford *s-cis* diene **2.41a**. However, subsequent readdition of the palladium catalyst, followed by  $\beta'$ -hydride elimination, generated *s-trans* diene **2.41b**. The two inseparable regioisomers were obtained in a 4:1 ratio, in a combined yield of 86%.

### Scheme 2.19



Principle methods for suppression of regioisomer formation include variation of the Pd-H scavenger (base),<sup>66b, 73</sup> and addition of silver salts.<sup>74</sup> If *in situ* suppression of isomer formation proves impossible, an alternative approach is catalytic isomerization of the *exo* (less substituted) product into the *endo* (more substituted) product via a subsequent reaction process,<sup>75</sup> or vice versa.<sup>76</sup> Another possibility is selective reduction of the olefin isomer mixture into a single diastereomer using Crabtree's iridium catalyst or palladium on carbon.<sup>77</sup> Crabtree's iridium catalyst is particularly useful because of its ability to achieve stereoselective reduction through chelation and its high reactivity which allows it to reduce tri- and tetrasubstituted olefins.<sup>77</sup>

### Intramolecular Heck Cascade

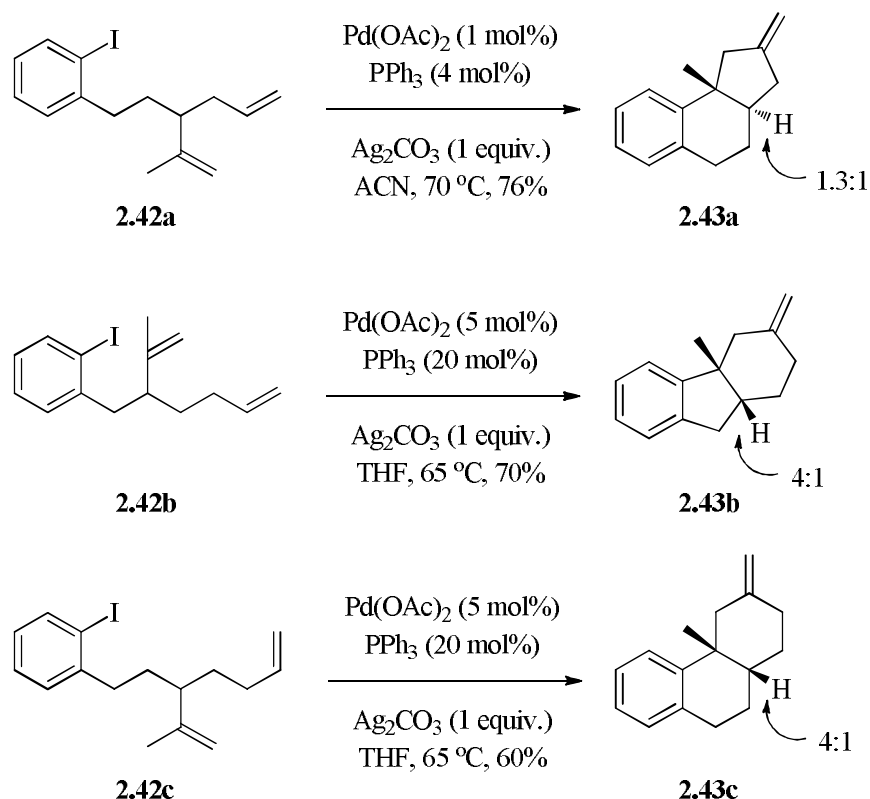
Cascade reactions, also known as domino reactions, are an important area of modern organic synthesis because they allow for a rapid increase in molecular complexity in a single step, from a relatively simple substrate.<sup>78</sup> In a cascade process two or more bond-forming reactions take place, under identical conditions, with the first transformation resulting in functionalities that allow the second transformation to proceed. Domino reactions are therefore an elegant, environmentally friendly method of combining multiple steps into a single transformation, effectively preserving resources and reducing waste production. Due to their cost effective ability to form complex structural motifs from relatively simple substrates, cascade reactions are well suited for both pharmaceutical and industrial settings. A Heck cascade reaction is a palladium-catalyzed process where two or more bond forming reactions occur in a

single step. This occurs when, following the first cyclization,  $\beta$ -hydride elimination is not possible, allowing the alkyl palladium species to participate in a second cyclization event. With two different regiochemical pathways available it is important to establish/identify differences between them, so that sequential carbopalladation occurs in a specific order. The most common method of differentiating between two or more competing cyclization pathways is ring size. Generally accepted rules include: intramolecular Heck cyclization being favored over intermolecular and medium-sized ( $n = 5-6$ ) ring formation being favored over small- ( $n < 5$ ) or large-sized rings ( $n > 6$ ).

For the purposes of this text we will focus primarily on two- step Heck cascade methods of forming 5- and 6-membered ring polycycles, from diene and enyne precursors. Beginning with formation of fused-, spiro- and (most importantly) bridged hydrocarbon polycycles, I'll then move into an in-depth examination of nitrogen containing polycycle formation and finally, synthesis of aryl-fused bridged *N*-heterocycles.

The Heck cascade reaction has been extensively applied toward the construction of hydrocarbon polycycles. Overman *et al.* have achieved efficient synthesis of tricyclic aryl-fused polycyclic hydrocarbons (**2.43a-c**) via a Heck cascade transformation (Scheme 2.20).<sup>79</sup> Using various acyclic dienyl aryl iodide starting materials (**2.42a-c**) they were able to obtain the corresponding fused polycyclic products in good yields as mixtures of stereoisomers. They were also pleased to observe complete suppression of *endo* olefin stereoisomer formation when a silver carbonate base was employed.

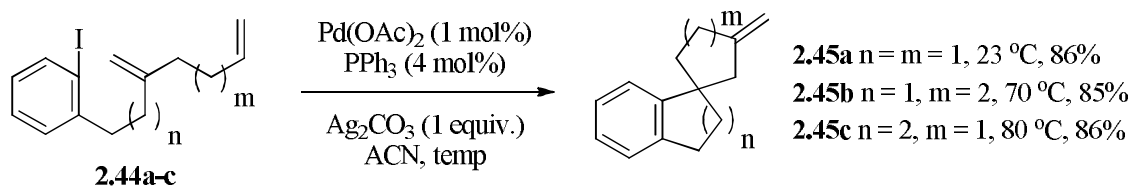
### Scheme 2.20



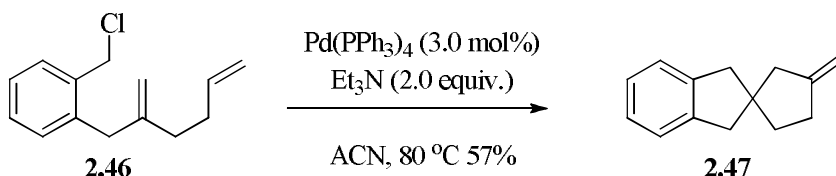
Intramolecular Heck cyclization of an alternative acyclic aryl iodide starting material (**2.44a-c**) afforded 5- and 6-membered ring spirocycles **2.45a-c** in good yields (Scheme 2.21).<sup>79</sup> Similar spirocycle **2.47** was obtained in a modest 57% yield, via Heck cyclization of benzyl chloride **2.46**.<sup>80</sup> Thirdly, an analogous Heck cascade process was applied to unsaturated enol triflate derivatives **2.48a-d** in order to synthesize a range of medium sized ring spiro polycycles (**2.49a-d**) in good to moderate yields (Scheme 2.22).<sup>79b, 81</sup> Interestingly, although a silver salt wasn't employed in the formation of spirocycles **2.47** and **2.49a-d**, olefin regioisomer formation wasn't observed.

### Scheme 2.21

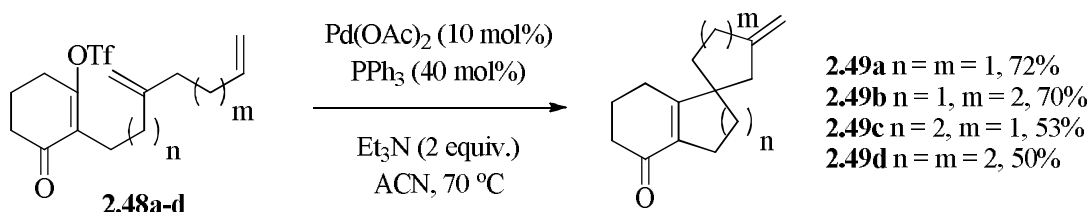




Scheme 2.22

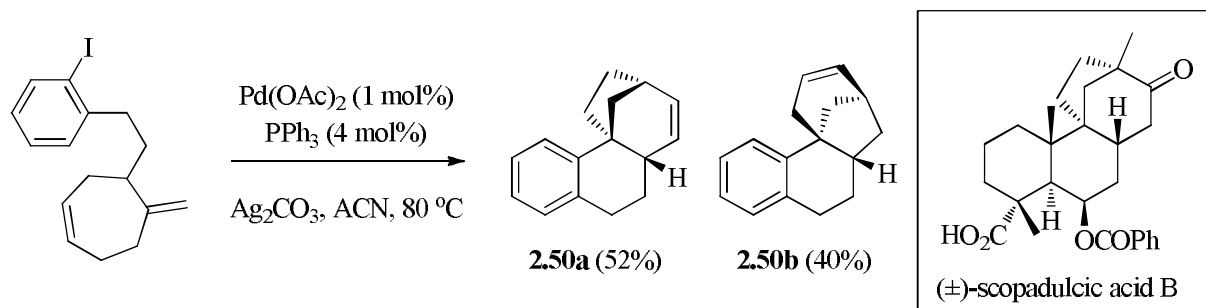


Scheme 2.23



Overman *et al.* have also employed the Heck cascade method to access bridged polycyclic hydrocarbons **2.50a** and **2.50b** (Scheme 2.24).<sup>79</sup> A scaled up version of this methodology was later utilized in the total synthesis of (±)-scopadulcic acid B<sup>82</sup> and A.<sup>83</sup>

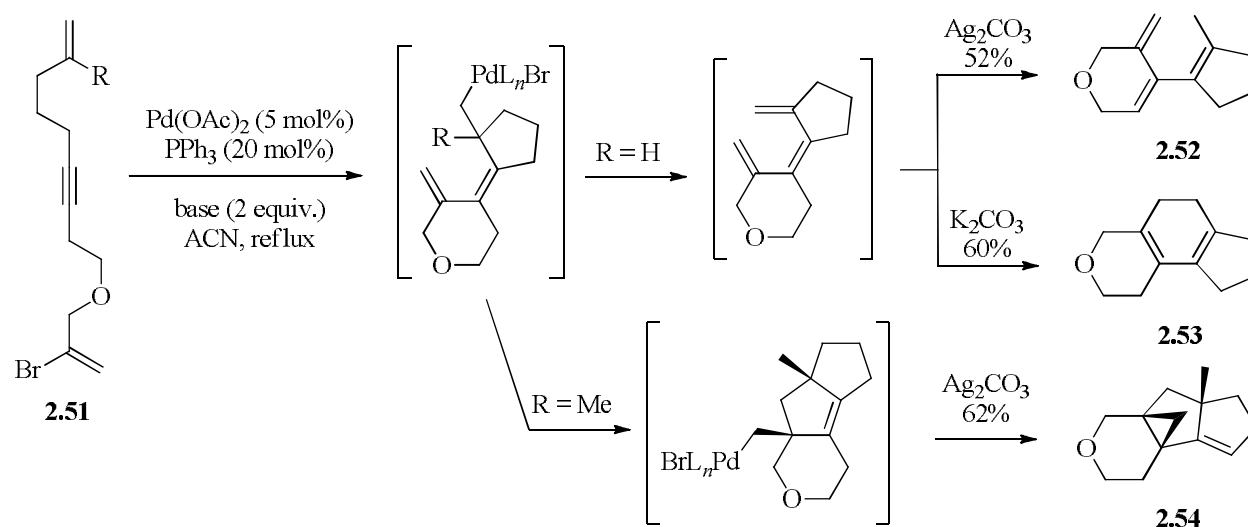
Scheme 2.24



Palladium-catalyzed domino Heck reactions have also been shown to be effective in the cyclization of enyne precursors. Using dienyne **2.51**, the de Meijere group has constructed various polycyclic scaffolds by variation of the base or R substituent (Scheme 2.25).<sup>84</sup> When a

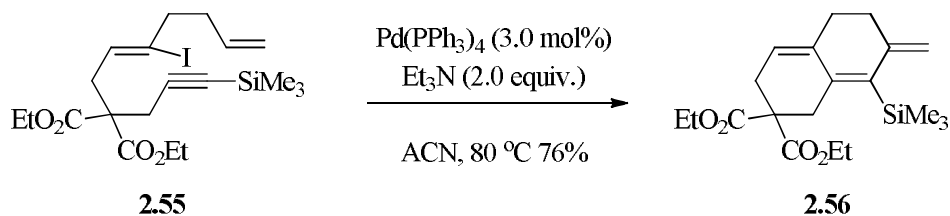
monosubstituted terminal olefin (**2.51**, R = H) was used, along with Ag<sub>2</sub>CO<sub>3</sub>, Heck cyclization afforded bicycle **2.52** in a 52% yield. However, when the silver salt was exchanged for K<sub>2</sub>CO<sub>3</sub>, the product went through an additional isomerization step to form fused tricycle **2.53**. Finally, when a 1,1-disubstituted olefinic substrate was used (R = Me), with a Ag<sub>2</sub>CO<sub>3</sub> base, a three-fold cyclization pathway led to tetracycle **2.54**. This diversity of products clearly demonstrates the substrate and reagent dependence of the intramolecular Heck cyclization process.

**Scheme 2.25**

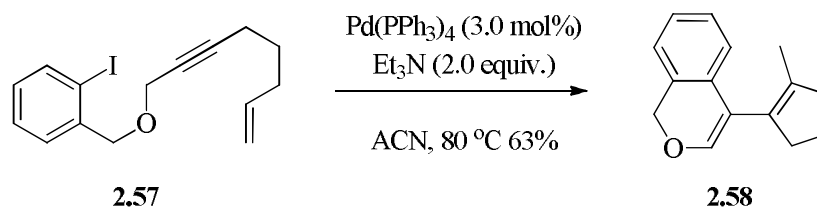


Heck cyclization of enyne precursors has also been demonstrated by Negishi *et al.*<sup>85</sup> Vinyl iodide **2.55** cyclized in a “zipper”-mode<sup>86</sup> two-fold cyclization to afford fused bicycle **2.56** in a 76% yield (Scheme 2.26). Polycycle **2.58** was also obtained in a 63% yield, via Heck cascade cyclization of enyne precursor **2.57**.<sup>85</sup>

**Scheme 2.26**

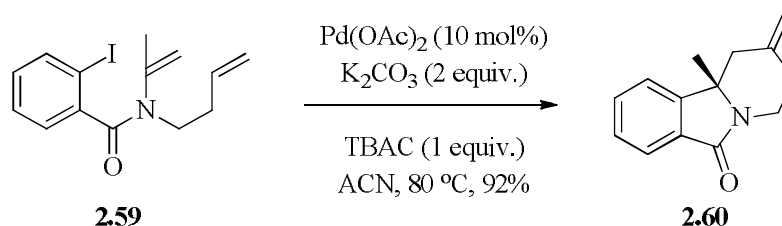


### Scheme 2.27

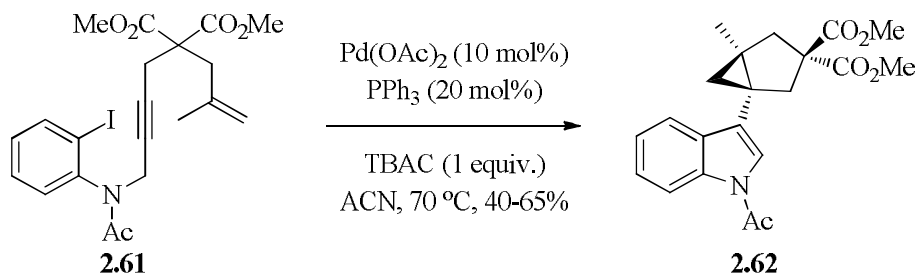


Of particular interest to my research is the less common application of Heck cascade chemistry to nitrogen containing heterocycle formation. Grigg *et al.* accomplished Heck cyclization of amide **2.59**, using Jeffery's ligandless Heck conditions (analogous to my work), to construct lactam **2.60** in a high 92% yield (Scheme 2.28).<sup>87</sup> Interestingly, contrary to the results observed in my research, isomerization of the *exo* olefin was avoided under these conditions. They were also able to obtain polycycle **2.62**, via a threefold cyclization of enyne precursor **2.61** (Scheme 2.29).<sup>88</sup>

### Scheme 2.28



### Scheme 2.29

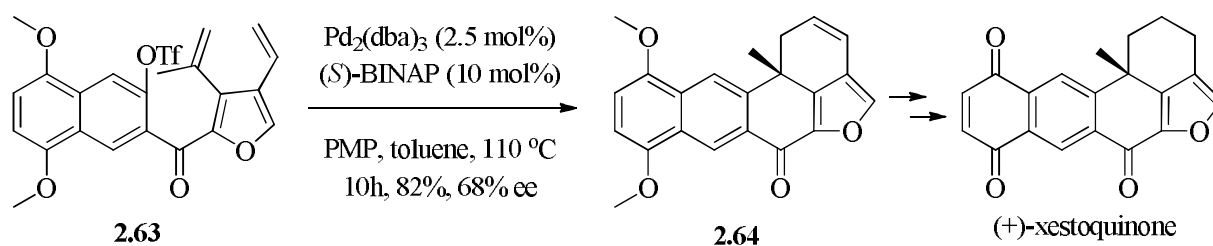


The Heck cascade reaction has also been employed as a key step in natural product total synthesis. Examples include use by the Keay group for the total synthesis of (+)-xestoquinone.<sup>89</sup>

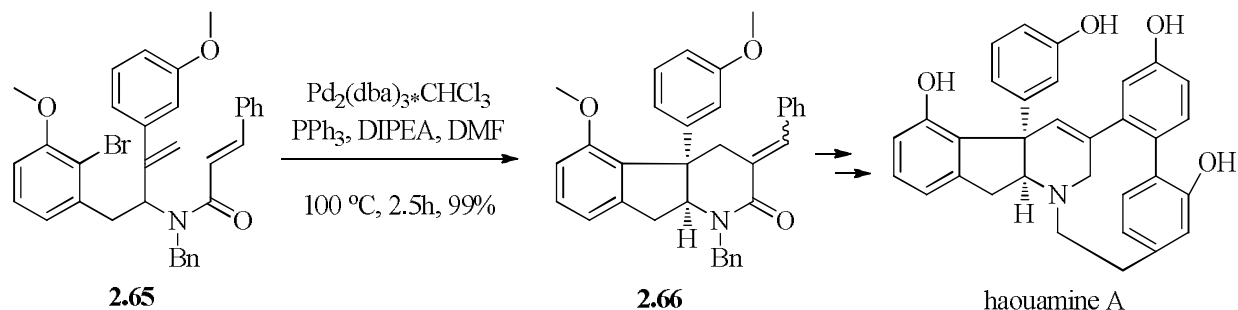
Two-fold Heck cyclization of aryl triflate **2.63** afforded (+)-xestoquinone precursor **2.64** in an 82% yield, with a new quaternary center (Scheme 2.30). Shibasaki *et al.* later improved on the method's stereoselectivity by employing an alternative chiral ligand.<sup>90</sup>

Heck cascade chemistry was also employed by Ishibashi *et al.* in their total synthesis of haouamine A (Scheme 2.31).<sup>91</sup> Cyclization of highly substituted amide **2.65** afforded lactam **2.66**, as a mixture of stereoisomers, in a nearly quantitative yield.

**Scheme 2.30**

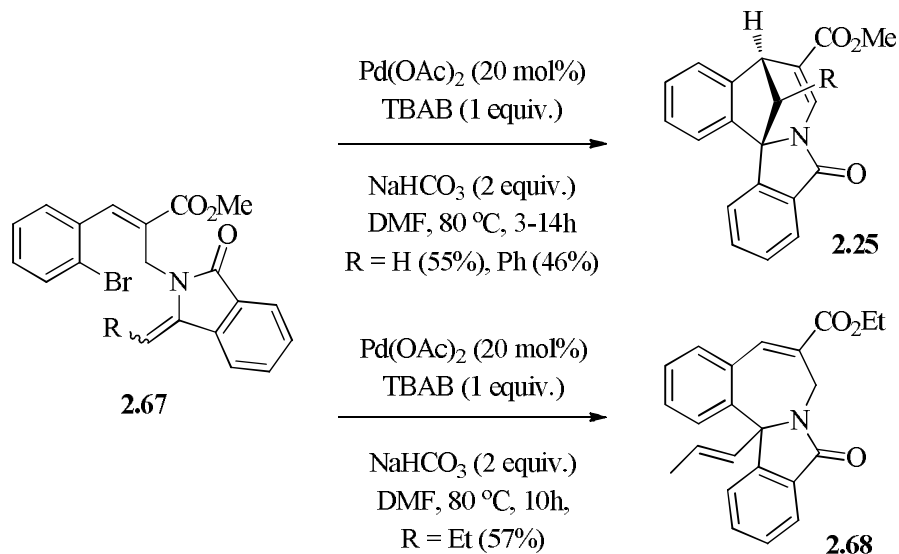


**Scheme 2.31**



Finally, the only example published thus far of bridged *N*-heterocycle formation, via a Pd-Heck cascade, is from the Kim group.<sup>92</sup> Using Jeffrey's ligandless Heck conditions,<sup>67</sup> they were able to synthesize novel pentacyclic benzoazepino[2,1,3]isoindole **2.25** from enamide precursor **2.67** (R = H, Ph) (Scheme 2.32). However, as expected, when a  $\beta$ -hydrogen was present following the first cyclization (**2.67**, R = Et), rapid  $\beta$ -hydride elimination terminated the Heck cascade to afford lactam **2.68** (Scheme 2.32).

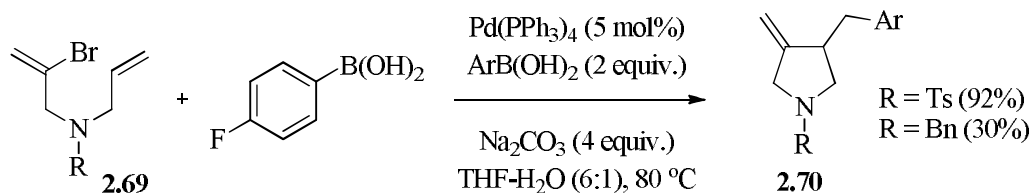
### Scheme 2.32



### Trapping of Organopalladium Intermediates

In most of the previously described Heck reactions, cascade cyclization is followed by a  $\beta$ -hydride elimination event; however, an attractive alternative involves trapping the alkyl palladium intermediate prior to elimination, via an anion capture process. Possible anion capture agents include formate ion,<sup>93</sup> zinc,<sup>87</sup> tin,<sup>94</sup> and boron<sup>95</sup> derivatives, CO<sup>96</sup> and more.<sup>97</sup> However, in all of these cases the substrate is designed so that  $\beta$ -hydride elimination is not possible, because elimination is typically kinetically favored over anion capture. Novel palladium-catalyzed cyclization of vinyl bromide **2.69**, terminated via Suzuki coupling, proceeded with suppression of  $\beta$ -hydride elimination to form pyrrolidine **2.70** (Scheme 2.33).<sup>98</sup> This unusual precedent is explained by neighboring group stabilization of the alkylpalladium intermediate via a tosyl oxygen, thereby suppressing  $\beta$ -hydride elimination and giving a 92% yield of pyrrolidine **2.70** (R = Ts). In order to test this working hypothesis, Heck cyclization was performed on an analogous benzyl protected substrate, affording a much lower 30% yield of Suzuki coupled product **2.70** (R = Bn).

### Scheme 2.33

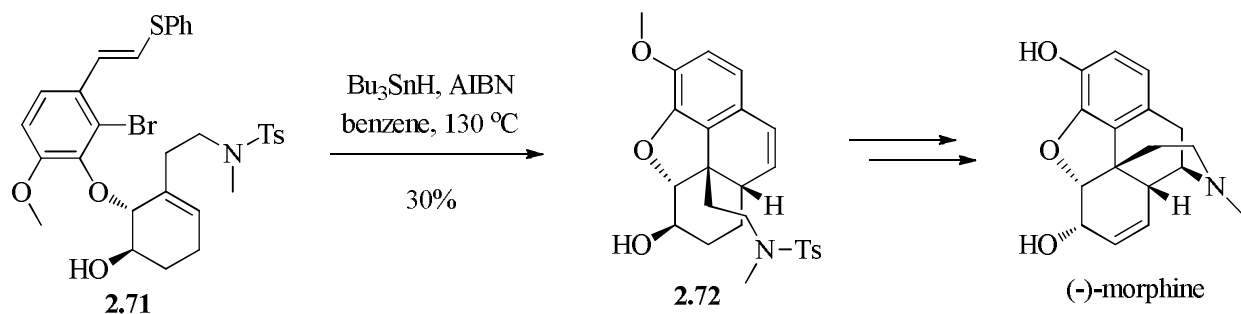


### 2.4 Radical Cascade Reaction

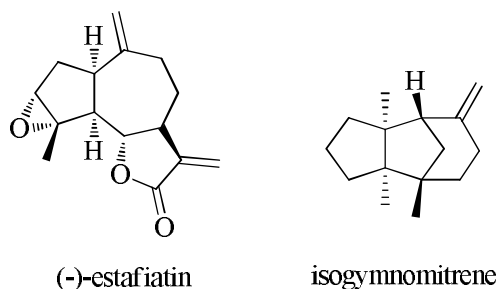
Intramolecular free radical cyclization has emerged as a powerful tool for heterocycle synthesis.<sup>99</sup> Major advantages to the radical process include functional-group tolerance, pH neutral conditions and their ability to be easily extended to a cascade process (without having to consider  $\beta$ -hydride elimination).<sup>78, 99-100</sup> What follows is a discussion of select radical cascade reactions, on diene and enyne substrates, to form fused and bridged polycyclic molecular scaffolds. This review of radical cascade chemistry is also limited to traditional AIBN/tin hydride protocols.

A seminal work in the radical cascade cyclization of diene precursors, published by Parker and Fokas, outlines their recent total synthesis of (-)-morphine (Scheme 2.34).<sup>22</sup> Aryl bromide intermediate **2.71** was treated with tributyltin hydride and AIBN at reflux in benzene to afford tetracyclic morphine precursor **2.72** in a 30% yield, with two new rings and all carbon quaternary centers set.

### Scheme 2.34



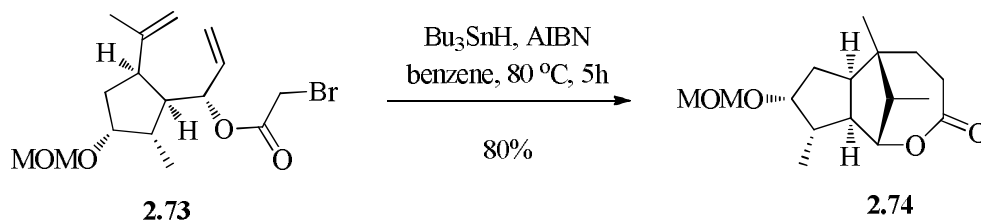
Radical cyclization of diene substrates has also been employed as a key step in the total synthesis of (-)-estafiatin<sup>101</sup> and isogymnomitrene (Figure 2.17).<sup>102</sup>



**Figure 2.17** Natural products obtained via a radical cascade reaction.

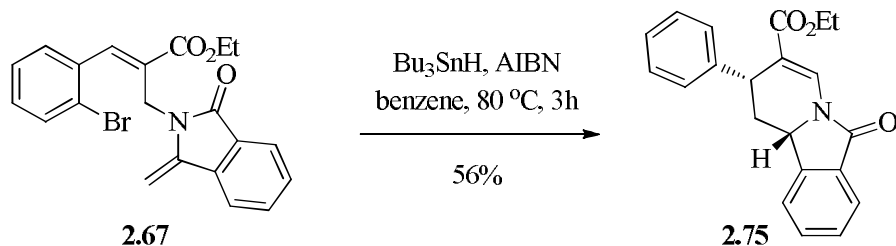
While attempting the total synthesis of (-)-estafiatin, Lee *et al.* obtained bridged *O*-heterocycle **2.74** via an unusual 8-*endo-trig*, 5-*exo-trig* cyclization pathway, affording diene **2.73** in an 80% yield (Scheme 2.35).<sup>103</sup> Interestingly the initial competing 5-*exo-trig* was not observed.

**Scheme 2.35**



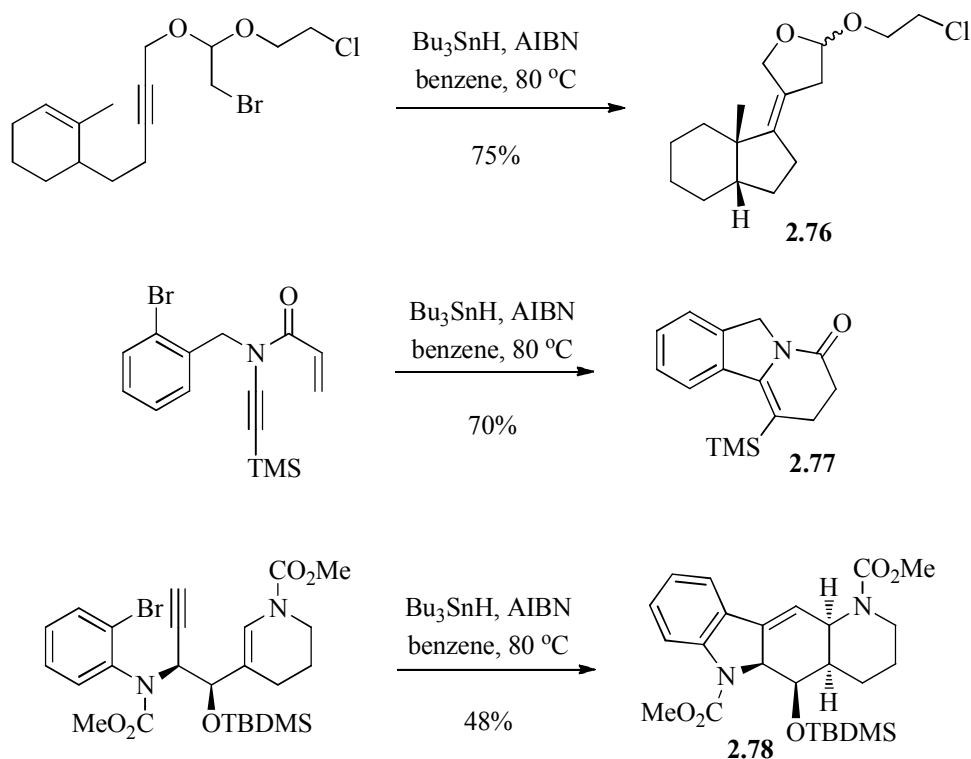
In spite of their relatively wide spread use in modern organic synthesis, radical cascade transformations have experienced only limited application in the formation of bridged *N*-heterocycles. As previously discussed, Kim *et al.* obtained a novel aryl-fused azabicyclooctane scaffold **2.68** via Heck cascade cyclization of Baylis-Hillman adduct **2.67** (R = H) (Scheme 2.32).<sup>92</sup> However, when that same substrate (**2.67**) was reacted under radical cyclization conditions they observed formation of unexpected fused polycycle **2.75** in a modest 56% yield (Scheme 2.36).<sup>104</sup> Together these two methods nicely highlight the synthetic potential of diversity oriented synthesis.<sup>105</sup>

### Scheme 2.36



Of particular interest to the context of this document are radical cascade cyclizations of enyne precursors and the formation of bridged *N*-heterocycles. Radical cyclization of an enyne substrate has been employed in the formation of various interesting scaffolds including polycycle **2.76** at a 75%,<sup>106</sup> **2.77** at 70%<sup>107</sup> and **2.78** at 48%<sup>108</sup> (Scheme 2.37). However, in each of these cases, cyclization proceeded through a less pertinent mechanism (through the alkene, then the alkyne).

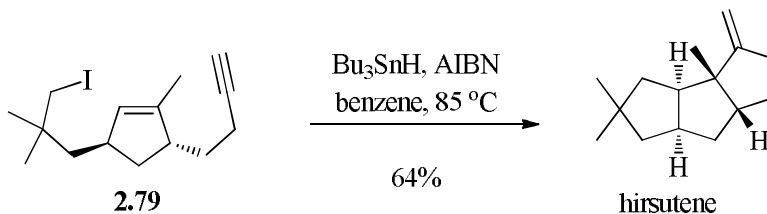
### Scheme 2.37





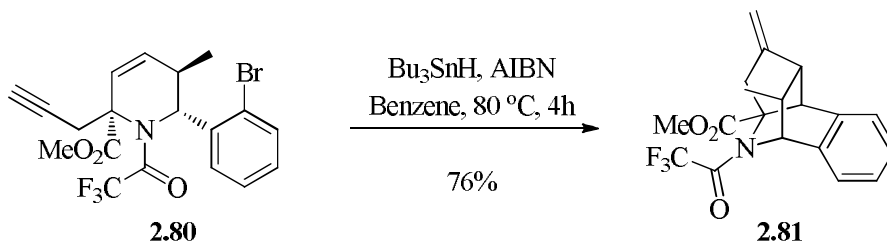
More applicable to my research, are radical cascade reactions which proceed via cyclization with the alkene first, then the alkyne. This reaction pathway was employed in the radical cascade cyclization of enyne **2.79**, concluding the total synthesis of hirsutene in a 64% yield (Scheme 2.38).<sup>109</sup>

**Scheme 2.38**



Synthesis of a bridged *N*-heterocycle scaffold, via radical cascade cyclization of an enyne precursor has recently been accomplished by Porco *et al.* (Scheme 2.39).<sup>38c</sup> Radical cyclization of enyne **2.80** proceeded with high regioselectivity through first a *6-endo-trig* then *5-exo-dig* cyclization to afford azabicyclooctane **2.81** in a 76% yield.

**Scheme 2.39**



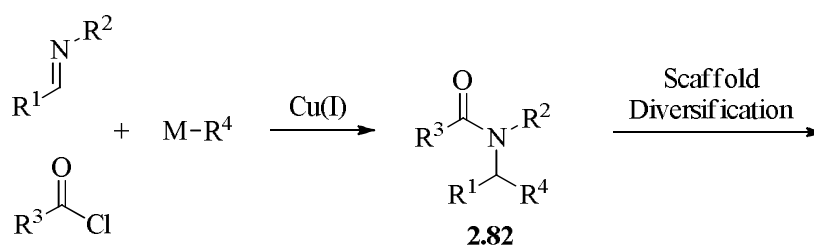
As can be seen from the previous review, radical cascade chemistry has experienced only limited application in the construction of bridged *N*-heterocycles. Seeing this as a significant gap in the literature our group has endeavored to develop our own radical cascade method.

## 2.5 Cu-Catalyzed Three-Component Coupling Reaction

A multicomponent reaction is a convergent process in which three or more starting materials combine to create a new, significantly more complex, product.<sup>44, 110</sup> The power of

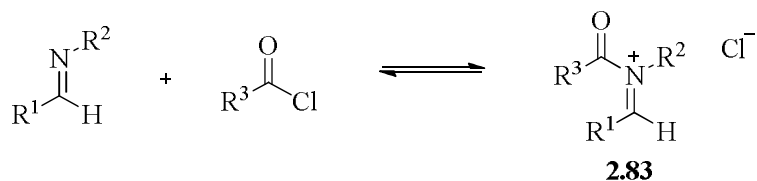
multicomponent reactions lies in their ability to achieve rapid and efficient synthesis of libraries of compounds, known as diversity oriented synthesis, simply by changing the starting materials.<sup>45, 111</sup> Transition metal-catalyzed multicomponent chemistry has emerged as an elegant and efficient method for forming complex and highly diverse structures in a one-pot fashion.<sup>110a</sup> Thus, multicomponent synthesis is considered a modern green chemical process. In addition, subsequent transformations are frequently employed to further enhance molecular complexity. Herein we review the development and application of copper-catalyzed three-component coupling reactions between imines, acid chlorides and an organometallic agent to form highly substituted amide products (**2.82**) (Scheme 2.40).

**Scheme 2.40**



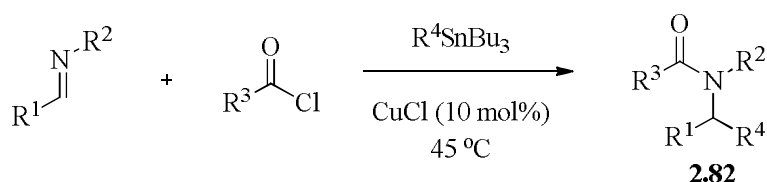
Recently, there has been a sharp increase in the popularity of imines in multicomponent chemistry due to their substrate-dependent reactivity and the vast array of commercially available aldehydes and amines, allowing access to innumerable imines and thereby diverse molecular scaffolds.<sup>112</sup> The lone-pair electrons on the imine nitrogen possess sufficient nucleophilic character such that, an electron rich imine will nucleophilically add into an electron deficient electrophile (acid chloride) affording *N*-acyliminium chloride intermediate **2.83** (Scheme 2.41).

**Scheme 2.41**



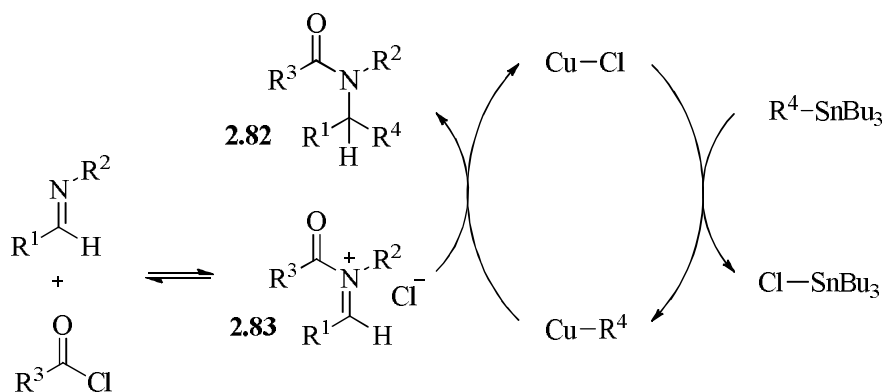
Taking advantage of this unique *N*-acyliminium chloride forming process, Arndtsen *et al.* have developed a series of novel amide forming three-component coupling reactions, using various organometallic agents.<sup>110a, 112</sup> The first of these reactions to be published utilized vinyl-, alkyl-, aryl- and heteroaryl-substituted organostannane reagents to achieve rapid synthesis of various amide products (**2.84**) (Scheme 2.42).<sup>113</sup>

**Scheme 2.42**



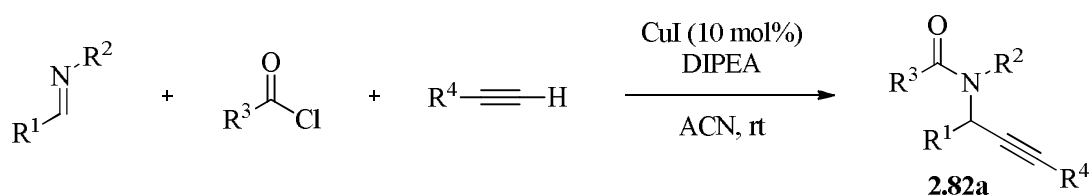
Mechanistically, the reaction begins with nucleophilic addition of the imine lone-pair into the acid chloride to form *N*-acyl iminium chloride intermediate **2.83** (Scheme 2.43). Concurrently, the organostannane transmetalates with the copper(I) catalyst to form an organocuprate. Finally, nucleophilic addition of the organocuprate into the *N*-acyl iminium chloride yields amide product **2.82**.

**Scheme 2.43**

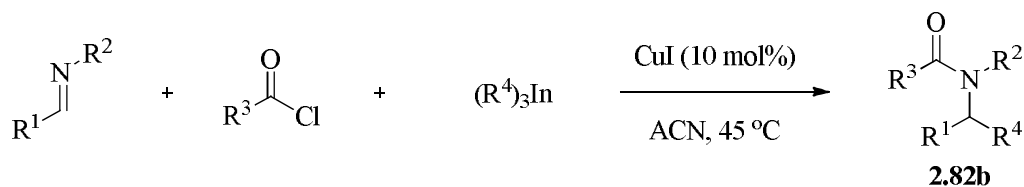


Similar approaches have been employed by Arndtsen *et al.* to couple other nucleophilic agents to the acyl iminium intermediate. One such example is the three-component coupling of an imine, alkyne and acid chloride to form highly substituted propargylamides (**2.82a**), using a CuI catalyst (Scheme 2.44).<sup>114</sup> A third variation is the use of organoindium nucleophiles to form  $\alpha$ -substituted amides (**2.82b**) and carbamates (Scheme 2.45).<sup>115</sup> Recently, Arndtsen *et al.* have developed a new strategy for the nucleophilic addition of organoboranes as a straightforward approach to  $\alpha$ -substituted amides (**2.82c**), without the need for activated imines (Scheme 2.46).<sup>116</sup>

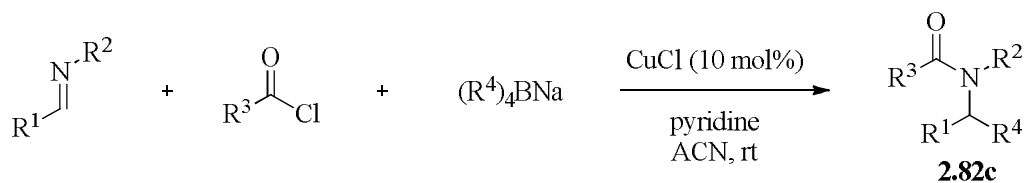
**Scheme 2.44**



**Scheme 2.45**



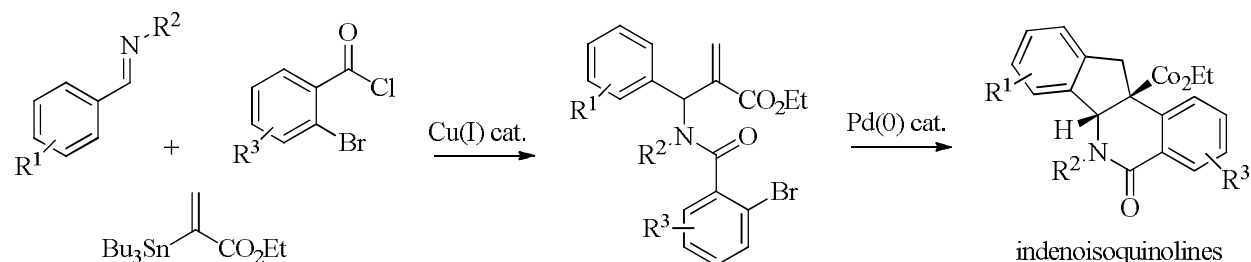
**Scheme 2.46**



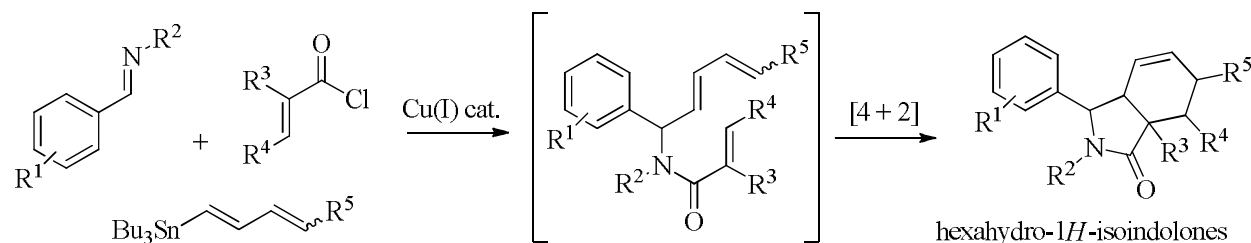
Since being developed by Arndtsen, this copper-catalyzed three-component coupling methodology has been expanded and applied as a key step in the synthesis of various complex heterocycles. Helena Malinakova *et al.* have developed new methodologies for forming

indenoisoquinolines (Scheme 2.47)<sup>117</sup> and hexahydro-1*H*-isoindolones (Scheme 2.48)<sup>118</sup> both of which were subsequently applied to combinatorial library synthesis.<sup>111</sup>

**Scheme 2.47**

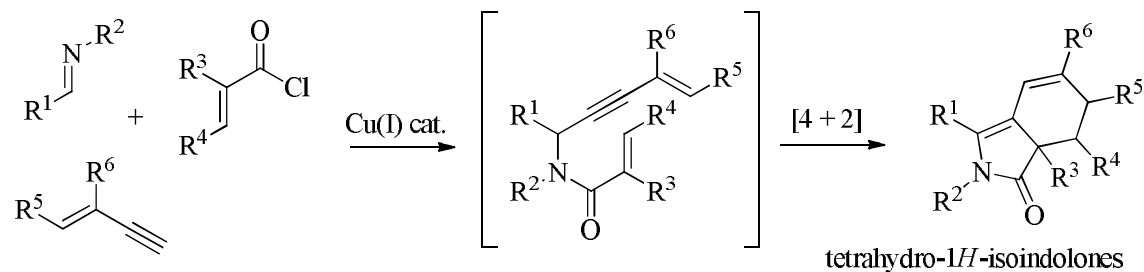


**Scheme 2.48**



Arndtsen's three-component method has also been recently employed in the synthesis of tetrahydro-1*H*-isoindolones, analogous to the Malinakova publication, by Huang *et al.* (Scheme 2.49).<sup>119</sup>

**Scheme 2.49**

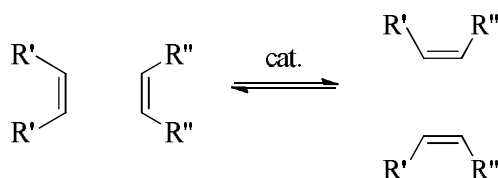


## 2.6 Ru-Catalyzed Olefin Metathesis

Olefin metathesis is an organometallic reaction where two double bonds come together and undergo a formal exchange of substituents (Scheme 2.50).<sup>120</sup> In recent years olefin

metathesis has experienced a tremendous increase in use due to the development of ruthenium-based catalysts.

**Scheme 2.50**



Grubbs *et al.* began investigating olefin metathesis in 1972 and by the early 1990's had demonstrated ruthenium(II) carbene complexes to be highly effective catalysts with both high reactivity and functional group tolerance.<sup>121</sup> Grubbs I catalyst,<sup>122</sup> introduced in 1995, was largely supplanted by the second generation Grubbs II catalyst<sup>123</sup> in 1999. While both catalysts are used for the same function in organic synthesis, the second generation catalyst possesses a higher activity (Table 2.1).<sup>123</sup>

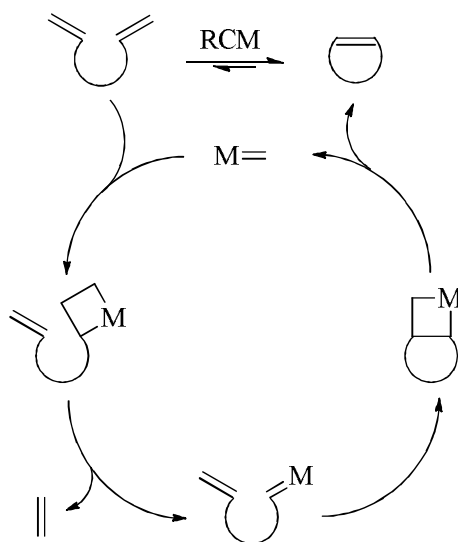
**Table 2.1**

<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">   Grubbs I </div> <div style="text-align: center;">   Grubbs II </div> </div>				
Substrate	Product	Time	Yield (%) with Grubbs I	Yield (%) with Grubbs II
		10 min	100	100
		10 min	20	100
		90 min	NR	90



The generally accepted mechanism for both cyclic and acyclic olefin cross metathesis proceeded through an alternating series of metallacyclobutanes and metal-carbene intermediates, with removal of ethylene being a major driving force (Scheme 2.51).

**Scheme 2.51**

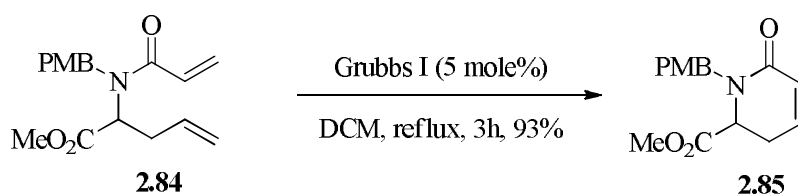


### Ring-Closing Metathesis

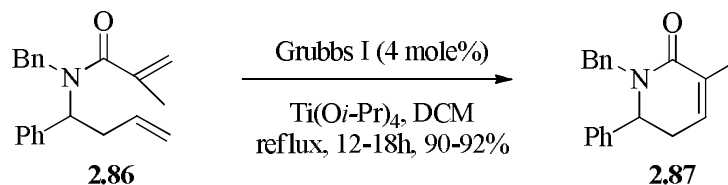
Ring-closing metathesis (RCM) is the intramolecular olefin metathesis of two tethered unsaturated fragments (alkene or alkyne) as shown in Scheme 2.51. This versatile cyclization process is capable of rapid, facile formation of almost any ring size (5 or greater), including previously challenging 7-8 membered rings and macrocycles. However, the RCM reaction is limited by sensitivity to the use of electron-deficient alkenes and the substitution pattern of the substrate, especially when using Grubbs I catalyst. For this reason RCM of  $\alpha,\beta$ -unsaturated amides has been poorly investigated. A limited number of reports found in the literature indicate that  $\alpha,\beta$ -unsaturated amides can be successfully cyclized with primary olefins, utilizing either

Grubbs I or II, the choice of which is highly substrate dependent.<sup>124</sup> RCM of acrylate adduct **2.84** proceeds rapidly using Grubbs I to generate a 93% yield of  $\alpha,\beta$ -unsaturated  $\delta$ -lactam **2.85** (Scheme 2.52).<sup>124e</sup> When methacrylate **2.86** was subjected to RCM conditions, the Grubbs I catalyst remained functional, however the reaction required the addition of a  $\text{Ti}(\text{OiPr})_4$  Lewis acidic additive to afford a 90-92% yield of  $\delta$ -lactam **2.87** (Scheme 2.53).<sup>124c</sup> Conversely, cyclization of *N*-acryloyl-allylic amine **2.88** in order to form  $\gamma$ -lactam **2.89**, while unsuccessful using Grubbs I, proceeded to an 82% yield using Grubbs II, without the need for an additive (Scheme 2.54).<sup>124d</sup>

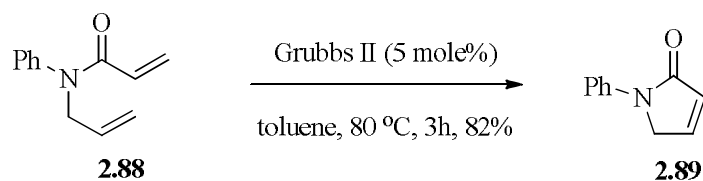
**Scheme 2.52**



**Scheme 2.53**



**Scheme 2.54**



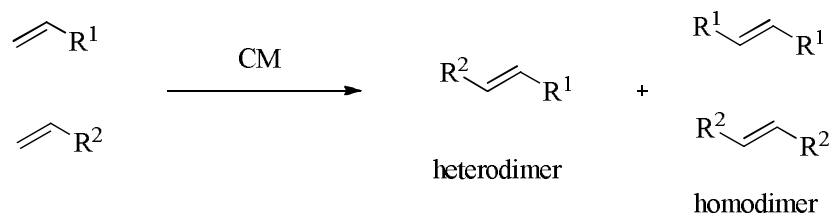
## Cross Metathesis

Olefin cross metathesis<sup>125</sup> (CM), in relation to other branches of olefin methathesis, is a relatively understudied synthetic method, due to low yields and unpredictable product regio- and



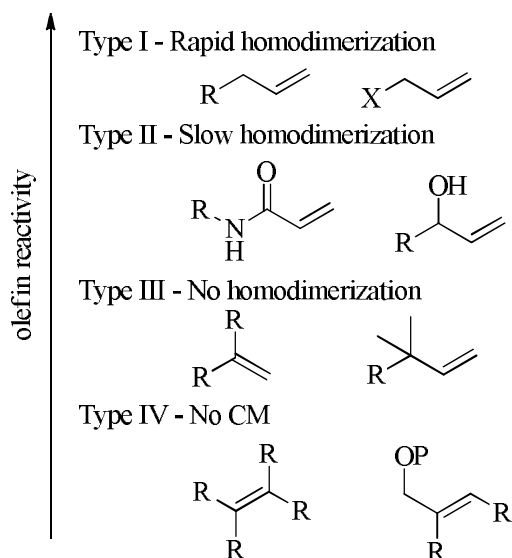
stereoselectivity. In addition, the CM of two different olefins is inevitably plagued by competing homodimerization reactions (Scheme 2.55).

**Scheme 2.55**



An investigation into CM of various olefin types led Grubbs *et al.* to form a general model for predicting homodimerization potential.<sup>126</sup> Olefins are ranked into four different types based on their affinity for homodimerization (Table 2.2). It is important to observe that these olefin type definitions require adjustment between different catalysts; however, in all cases steric bulk and electronic deficiency will deactivate the reaction.<sup>126</sup>

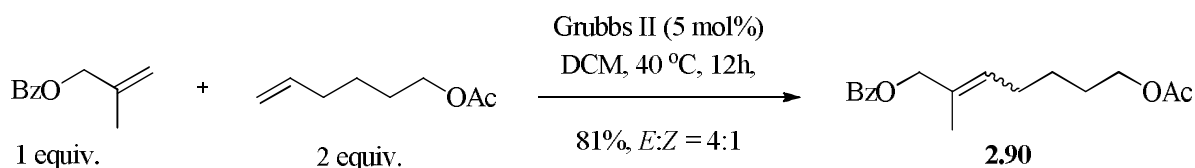
**Table 2.2**



One method for improving the selectivity in CM is to couple two different types of olefins. This is particularly true when coupling a Type I and Type III olefin. Grubbs demonstrated this selectivity by coupling a functionalized 1,1-disubstituted olefin with a

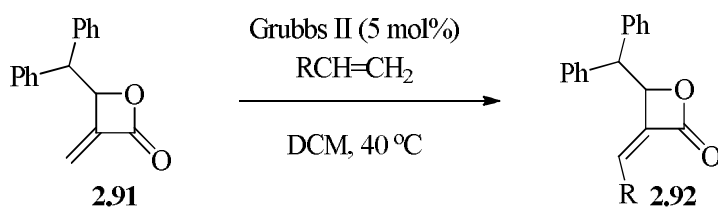
monosubstituted terminal, to afford CM product **2.90** in a 81% yield (Scheme 2.56).<sup>127</sup> This good yield was achieved with a low stoichiometric ratio of the two olefins and quantitative recovery of the unreacted disubstituted olefin starting material.

**Scheme 2.56**



Selective CM has also been realized by Raju and Howell between methylenexetanone **2.91** and various terminal olefins to form alkylideneoxetanones (**2.92**) in good yields with high *Z:E* stereoselectivity (Table 2.3).<sup>128</sup> The surprising high yields, with only 1.5 equivalents of the CM partner, nicely demonstrate the heterodimerization selectivity of Type I –Type III CM. The unexpected high *Z*-stereoselectivity observed is hypothesized to arise due to the steric effects of the  $\text{CHPh}_2$  substituent directing the catalyst to the opposite face of the lactone and the alkyl olefin substituent toward the carbonyl.

**Table 2.3**



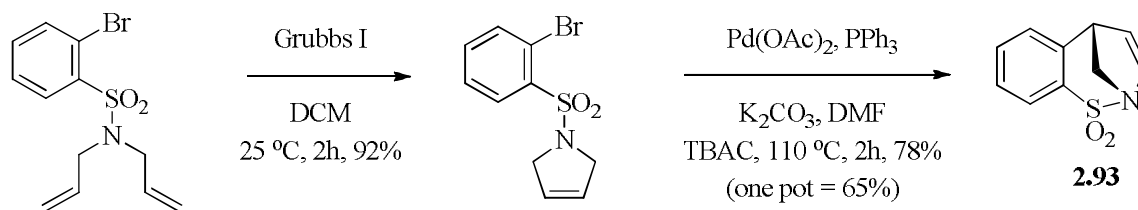
Entry	R	Yield (%)	<i>Z:E</i>
1	$(\text{CH}_2)_2\text{OAc}$	84	>20:1
2	$(\text{CH}_2)_3\text{OAc}$	90	>20:1
3	$(\text{CH}_2)_4\text{OAc}$	85	14:1
4	$(\text{CH}_2)_8\text{OAc}$	84	>20:1
5	Ph	55	>20:1
6	$(\text{CH}_2)_2\text{CH}_3$	94	11:1
7	$(\text{CH}_2)_2\text{Br}$	93	>20:1

## Sequential RCM/Heck cyclization

Separately, ruthenium catalyzed ring-closing metathesis and palladium-catalyzed Heck cyclization have proven to be robust methods capable of forming a vast array of ring systems. Therefore, the natural conclusion over the past several years has been to combine these two methods in a sequential or one-pot fashion, in order to achieve rapid construction of highly substituted *N*-heterocyclic scaffolds.<sup>129</sup> Outlined below are recent applications of sequential RCM/Heck catalysis in the preparation of novel bridged scaffolds and natural product synthesis.

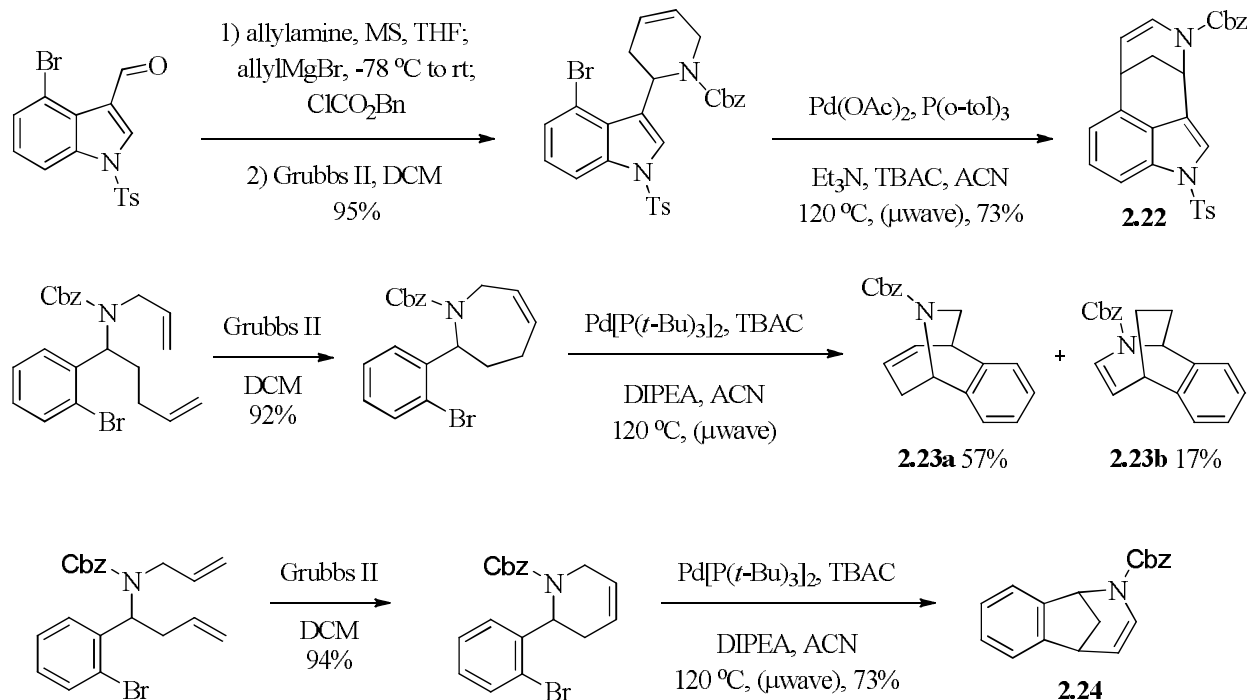
One of the early pioneers, Grigg *et al.*, has described a sequential olefin metathesis – intramolecular Heck reaction for forming aryl-fused bridged *N*-heterocycles including **2.93** in a 78% yield (Scheme 2.57).<sup>130</sup> This methodology was later adapted into a one-pot reaction using a polymer-bound palladium catalyst.<sup>131</sup> Evans *et al.* then utilized this method to access analogous aza-bridged compounds.<sup>132</sup>

**Scheme 2.57**



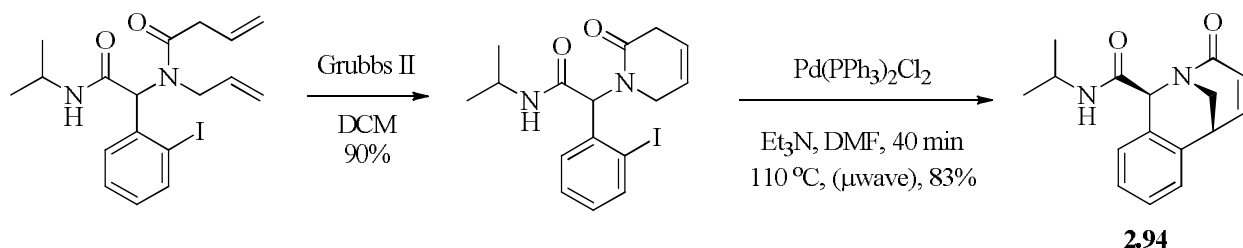
Sequential RCM/Heck reactions have also been extensively applied by Martin *et al.* in their formation of diverse bridged *N*-heterocyclic scaffolds (**2.22-2.24**) (Scheme 2.58).<sup>44, 110b</sup> An important element of Martin's work is the presence of reactive functionalities on the bridged core that can be further diversified into a collection of biologically active pharmaceutical agents. This methodology has recently been applied to combinatorial library synthesis, affording 124 analogues of bridged *N*-heterocyclic **2.24**, several of which expressed promising biological activity (Scheme 2.58).<sup>45</sup>

**Scheme 2.58**



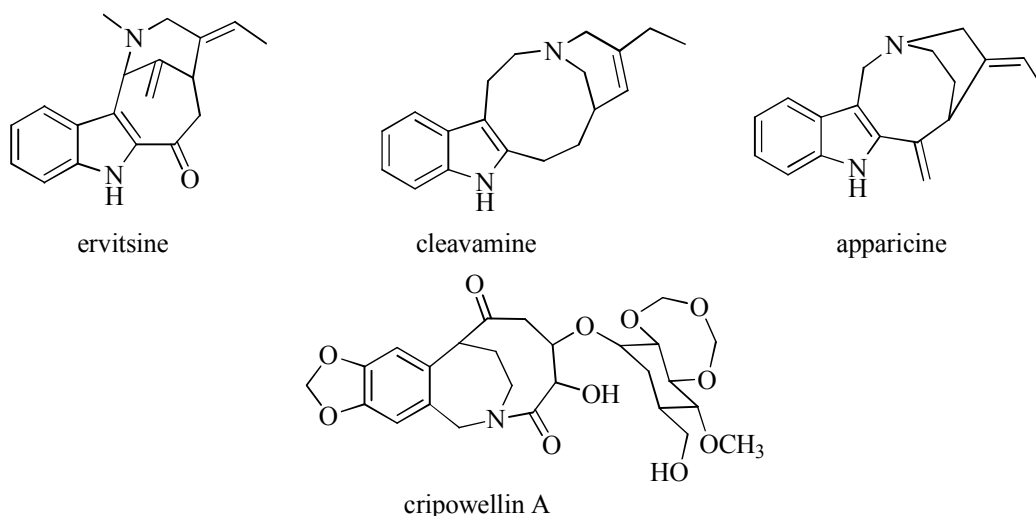
A similar RCM/Heck sequence was used by Judd *et al.* in their construction of novel bicyclic lactam scaffold **2.94** (Scheme 2.59).<sup>133</sup>

**Scheme 2.59**



In addition to methodology development and library synthesis an RCM/Heck sequence has been employed as a key step in the total synthesis of various naturally occurring alkaloids including ervitsine,<sup>134</sup> cleavamine,<sup>135</sup> apparicine<sup>136</sup> and cripowellins A (Figure 2.18).<sup>137</sup>

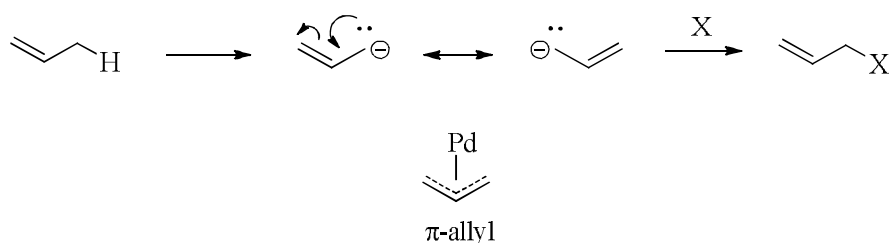
**Figure 2.18**



## 2.7 Functionalization of Allylic C-H Bonds

Allylic functionalization (allylic C-H activation) has recently emerged as a powerful and popular synthetic tool for installing reactive functionalities in the allylic position of an unactivated olefin. An  $sp^3$  C-H, adjacent to an olefin, is described as allylic because the unpaired electron(s) formed in the reaction intermediate are delocalized, thereby lowering the energy of that intermediate and making the initial C-H bond weaker than ordinary  $sp^3$  C-H bonds (Scheme 2.60). When transition metal catalysis is employed, this intermediate forms a highly stabilized  $\pi$ -allyl intermediate.

**Scheme 2.60**



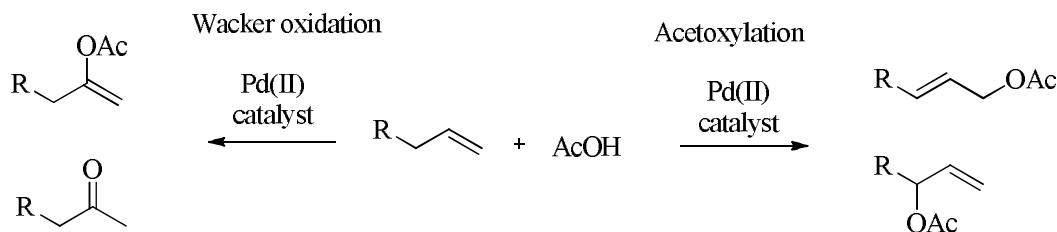
### Acetoxylation

Allylic acetates are an important intermediate in organic synthesis due to their ability to undergo metal-catalyzed replacement of the acetate with various nucleophiles. For this reason

there has been extensive interest in developing broadly applicable methods of installing an acetate substituent in the allylic position of an unactivated olefin (Scheme 2.70).<sup>138</sup> Described herein are relevant palladium-catalyzed methods of allylic acetoxylation.

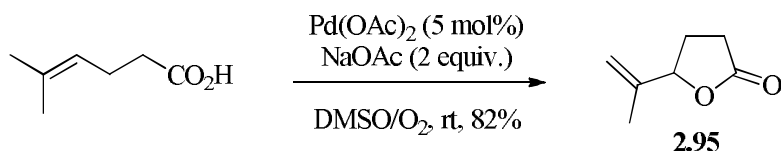
One of the challenges faced when developing a catalytic acetoxylation reaction is the formation of an undesired Wacker oxidation product (Scheme 2.61).<sup>139</sup> The Wacker oxidation is a palladium (II)-catalyzed reaction which proceeds via Markovnikov oxypalladation/ $\beta$ -hydride elimination to afford a vinyl acetate and/or ketone product (Scheme 2.61). Alternatively, acetoxylation is thought to be achieved through nucleophilic addition to a  $\pi$ -allyl palladium intermediate to give an allyl acetate product. Due to the similarity between these two reactions, achieving selective acetoxylation can be difficult.

**Scheme 2.61**



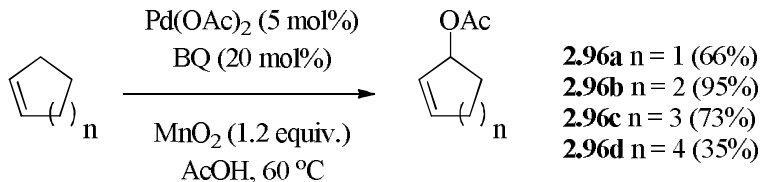
Intramolecular catalytic acetoxylation, to form unsaturated lactone **2.95** was demonstrated by Larock and Hightower in 1993 using  $\text{Pd}(\text{OAc})_2$  in DMSO and molecular oxygen as an oxidant (Scheme 2.62).<sup>140</sup> Under these conditions they were able to synthesize 5- and 6-membered lactones, with a preference for  $\sigma$ -bond formation at the internal olefinic carbon center. This versatile method was capable of forming monocyclic, fused, spiro and bicyclic lactones in generally high yields (Scheme 2.62). Since that time many more analogous reaction conditions have been developed that are capable of medium-size ring lactonization.<sup>141</sup>

**Scheme 2.62**



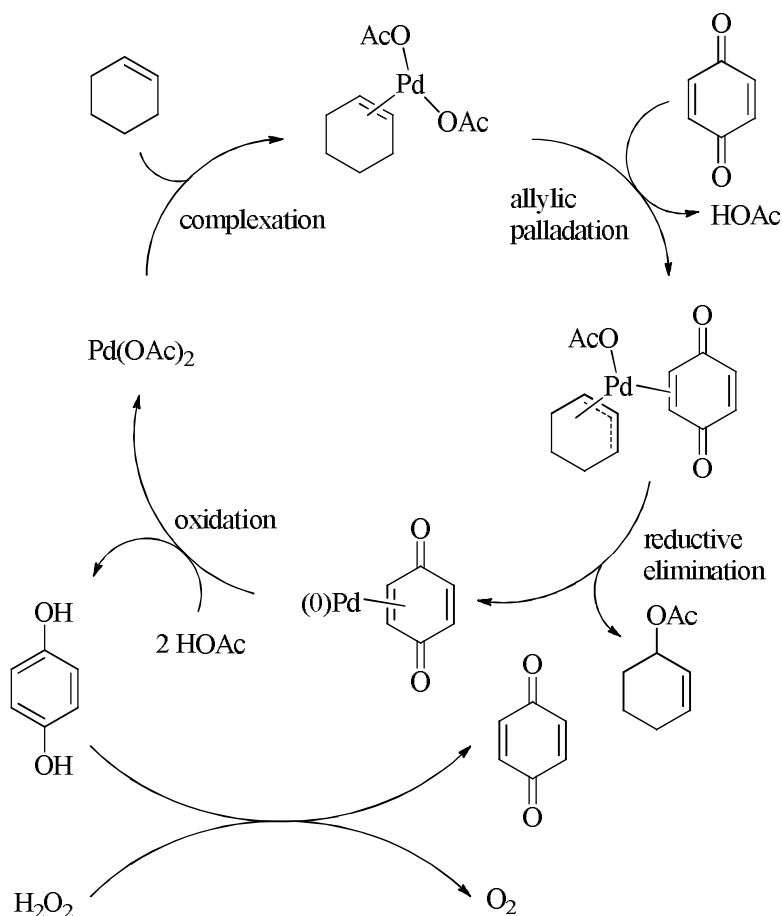
Intermolecular acetoxylation of alkenes is also of great interest to the synthetic community. Heumann and Akermark have demonstrated the use of  $\text{Pd(OAc)}_2$  and benzoquinone (BQ) in AcOH, with  $\text{MnO}_2$  as a stoichiometric oxidant, to access acetoxyated cycloalkenes **2.96a-d** (Scheme 2.63).<sup>142</sup> Akermark *et al.* later expanded their method to include the use of alternative oxidants including  $\text{H}_2\text{O}_2$  and TBHP.<sup>141a</sup> A large scale variant of the  $\text{Pd(OAc)}_2$ -BQ- $\text{H}_2\text{O}_2$  acetoxylation system was published one year later.<sup>143</sup> Other methods including a  $\text{PdCl}_2$ - $\text{AgOAc}$ - $\text{TeO}_2$ -TBHP catalytic system,<sup>144</sup> nitro-complexes of palladium(II)<sup>145</sup> and  $\text{Pd(OCOCF}_3)_2$  with stoichiometric BQ<sup>146</sup> have also been successfully employed.

**Scheme 2.63**



The mechanism for allylic acetoxylation of cyclohexene has been elucidated by Bäckvall and Akermark, revealing four major steps (Scheme 2.64).<sup>145e, 147</sup> First, the olefin is activated by coordination of the palladium(II) acetate. Secondly, an allylic hydrogen is removed, followed by BQ coordination to afford a  $\pi$ -allyl palladium BQ complex. Reductive elimination then produces the allylic acetate and  $\text{Pd(0)}$ . The final step in the catalyst cycle is regeneration of the  $\text{Pd(II)}$  catalyst with acetic acid. The BQ is also regenerated, via the stoichiometric oxidant.

**Scheme 2.64**

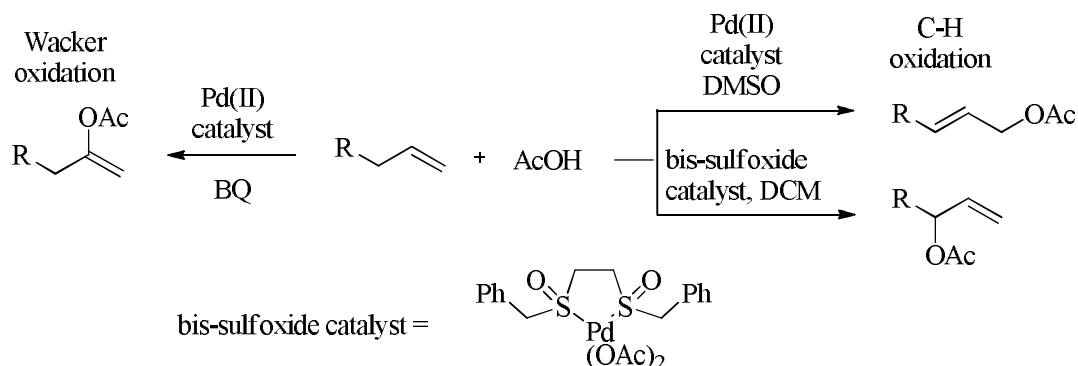


Christina White *et al.* have conducted an extensive investigation into the acetoxylation of terminal olefins. Using  $\text{Pd}(\text{OAc})_2$ , BQ, a novel bisulfonide ligand and dimethyl sulfoxide (DMSO) the White group was able to block the formation of the Wacker oxidation product and achieve selective formation of either the linear or branched acetoxylation product (Scheme 2.65).<sup>139, 148</sup> Under standard conditions ( $\text{Pd}(\text{OAc})_2$ , benzoquinone (BQ) and  $\text{AcOH}$ ) they obtained the Wacker oxidation product; however addition of DMSO afforded the linear (*E*)-allylic acetate with high regio- and stereoselectivity.<sup>139</sup> Their working hypothesis, that this result was due to the sulfoxide ligation of palladium, was further supported when they demonstrated that a bis-sulfoxide  $\text{Pd}(\text{II})$  acetate complex (in DCM) would also achieve allylic C-H oxidation. Although, in this case they observed nearly exclusive formation of the branched product, with



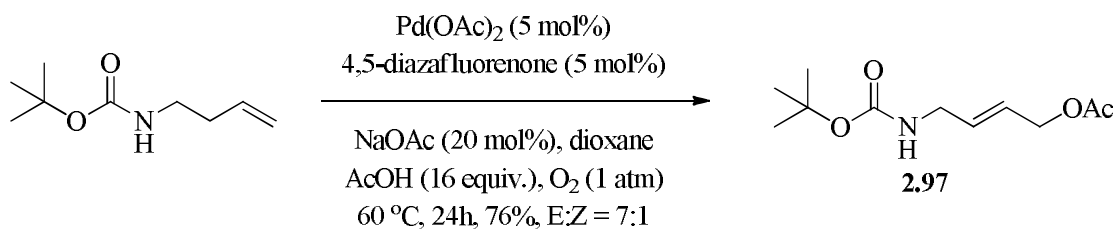
<1% of the Wacker oxidation product.<sup>139</sup> Mechanistic studies revealed an analogous reaction pathway to that previously discussed.<sup>149</sup>

### Scheme 2.65



In addition to the bisulfonide ligand utilized by White, other research groups have successfully demonstrated the use of ligands such as bipyrimidine,<sup>150</sup> 4,5-diazafluorenone<sup>151</sup> and thioethers.<sup>152</sup> In 2010 Stahl and coworkers obtained modest yields of linear acetoxyated products, including **2.97** using a 4,5-diazafluorenone ligand and 1 atm of oxygen as the oxidant (Scheme 2.66).<sup>151</sup> Mechanistic studies revealed that the new ligand facilitated reductive elimination, thereby eliminating the need for benzoquinone. Successful acetoxylation of internal olefins was recently achieved using sodium perborate<sup>153</sup> or iodonium salts<sup>154</sup> as oxidants.

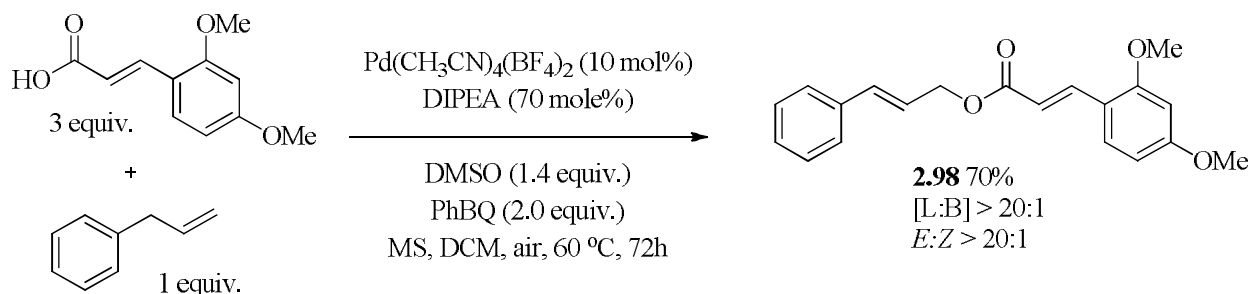
### Scheme 2.66



The intermolecular acetoxylation method has recently been extended to the formation of more complex allylic esters, including **2.98**, by White,<sup>155</sup> and Jean Le Bras,<sup>156</sup> independently

(Scheme 2.67). These reactions allowed the coupling of a wide range of aryl and alkyl carboxylic acids to a terminal olefin yielding linear (E)-allylic esters in high yields.

### Scheme 2.67

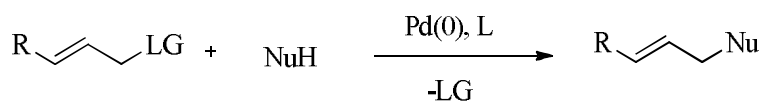


As demonstrated, acetoxylation is a powerful method for installing a leaving group at the allylic position of an unactivated olefin. Furthermore, through careful selection of reaction conditions high regio- and stereoselectivity can be achieved. However, thus far the method has only been applied to relatively simple substrates. Notable exceptions include acetoxylation of naturally occurring terpenes,<sup>157</sup> and a total synthesis of 6-deoxyerythronolide B.<sup>158</sup> Future efforts should take advantage of this gap in the literature by attempting the acetoxylation of complex *N*-heterocyclic scaffolds.

### Tsuji-Trost reaction

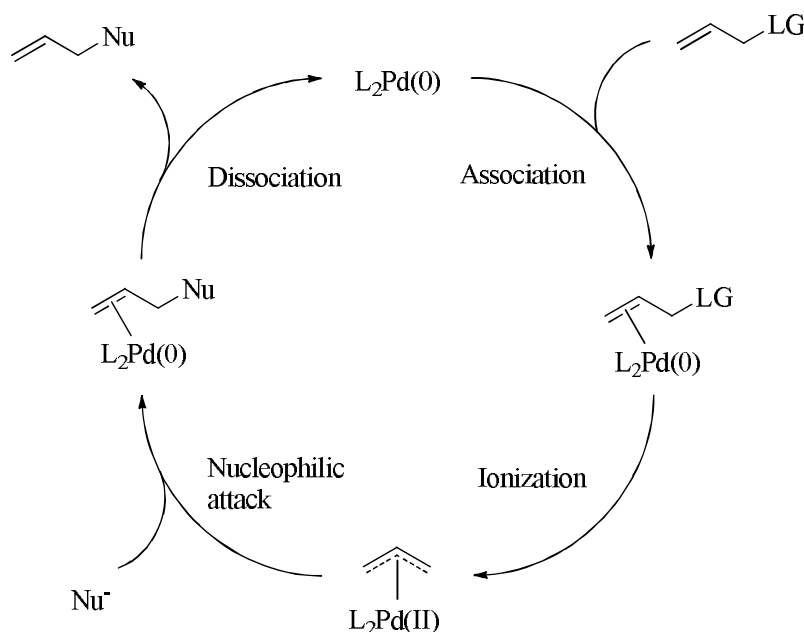
The palladium-catalyzed Tsuji-Trost reaction is a versatile tool widely used in modern organic synthesis (Scheme 2.68).<sup>159</sup> Tsuji *et al.* first reported the reaction in 1965 and Trost *et al.* later began expanding the method, incorporating phosphine ligands, various nucleophiles and leaving groups and later asymmetric synthesis.<sup>160</sup>

### Scheme 2.68



One of the major advantages to the Tsuji-Trost reaction is that it typically occurs under mild conditions, with high and predictable stereo-, regio- and chemoselectivity.<sup>161</sup> As stated before, allyl acetates (among others) are commonly employed substrates. Additionally, the method tolerates a wide variety of hard and soft nucleophiles (i.e. malonates). The catalytic cycle begins with coordination of Pd(0) with the olefin of the allylic substrate, forming an  $\eta^2$  complex (Scheme 2.69). Oxidative addition then expels the leaving group (ionization) and forms an  $\pi$ -allyl complex. Finally, nucleophilic attack, followed by dissociation of the Pd(0) affords the product. If the  $\pi$ -allyl complex is unsymmetric, substitution will typically occur at the less hindered allylic position.

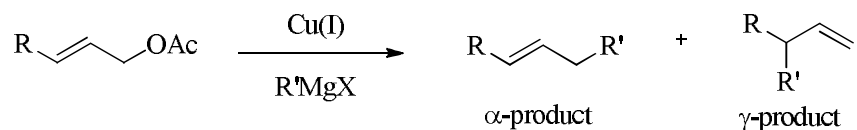
**Scheme 2.69**



Allyl acetates are also useful as substrates in copper(I)-catalyzed cross coupling reactions with a Grignard reagent (Scheme 2.70).<sup>162</sup> Regioselectivity of carbon-carbon bond formation is an important aspect of this catalytic process, with various factors controlling formation of either

the  $\alpha$  or  $\gamma$  product.<sup>162b-d</sup> This reaction is also highly stereoselective, with the nucleophile adding exclusively to the opposite side, with respect to the leaving group.<sup>162b</sup>

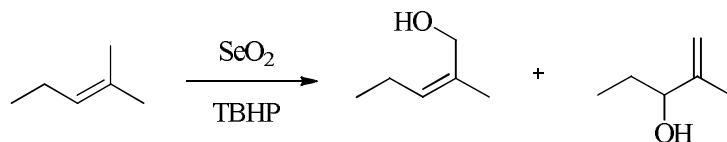
#### Scheme 2.70



#### Other Allylic Functionalization Methods

Other methods of functionalizing the allylic position of an olefin include selenium dioxide oxidation, radical allylic bromination and Ireland-Claisen rearrangement. Selenium dioxide allylic oxidation is a classic method for insertion of oxygen into an allylic C-H bond via a pericyclic process (Scheme 2.71).<sup>163</sup> In spite of this reactions classic roots and undesired by-products it is still widely used in natural product synthesis.<sup>164</sup>

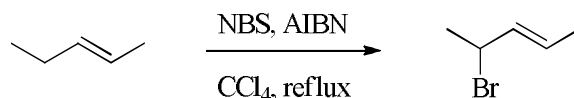
#### Scheme 2.71



Allylic bromination (Wohl-Ziegler reaction) is yet another commonly used method of allylic functionalization, this time with even earlier origins (Scheme 2.72).<sup>165</sup> Standard conditions use *N*-bromosuccinimide as a bromine source, AIBN or benzoyl peroxide as a radical source and anhydrous  $CCl_4$  as a solvent, at reflux. Once radical initiation has occurred the allylic hydrogen is removed forming a resonance stabilized radical intermediate. Termination with a bromine radical then gives the allylically substituted product. If more than one allylic position is available, bromination will occur at the more substituted position, because of the stabilization incurred on the corresponding radical intermediate. One major drawback is the need for  $CCl_4$ , a

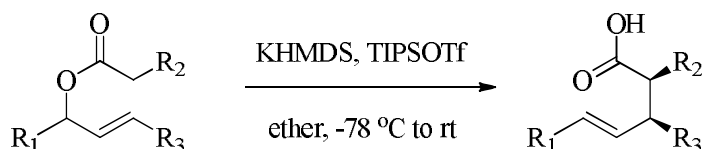
major environmental pollutant. However, just as with the other methods, allylic bromination continues to be a powerful tool in natural product synthesis.<sup>166</sup>

#### Scheme 2.72



The final allylic functionalization method to be discussed herein is the Ireland-Claisen rearrangement (Scheme 2.73).<sup>167</sup> The Ireland-Claisen rearrangement is a recent variation (introduced in 1972) of the classic Claisen rearrangement. This method has two major advantages including easily prepared allylic esters and high stereoselectivity (including chirality transfer).<sup>167-168</sup> The reaction begins with base-catalyzed enolate formation, followed by a concerted Claisen-like rearrangement and finally hydrolysis to afford the carboxylic acid product. McIntosh, a leading expert on the Ireland-Claisen rearrangement, has recently begun successfully applying this method as a key step in natural product synthesis.<sup>169</sup>

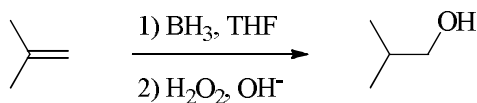
#### Scheme 2.73



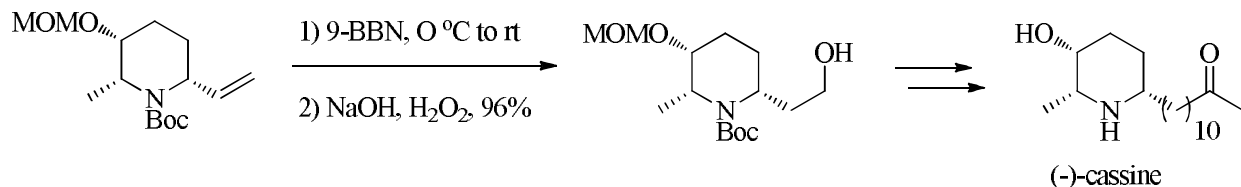
### 2.8 Hydroboration Reaction

The hydroboration-oxidation reaction is a classic method of converting alkenes into alcohols (Scheme 2.74). This two-step process begins with *syn* addition of BH<sub>3</sub> in an anti-Markovnikov fashion. Addition of hydrogen peroxide then produces the alcohol product. Hydroboration is a powerful tool widely used in organic synthesis as demonstrated by Makabe *et al.* in their total synthesis of (-)-cassine (Scheme 2.75).<sup>170</sup>

### Scheme 2.74



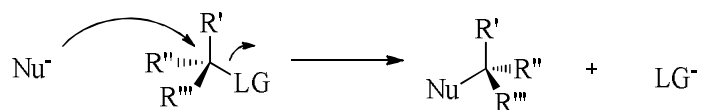
### Scheme 2.75



## 2.9 Nucleophilic Substitution Reaction

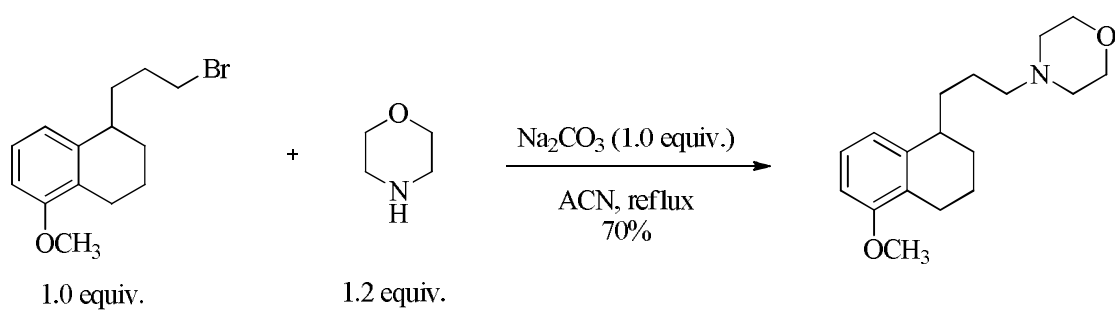
The nucleophilic substitution reaction, one of the cornerstones of organic synthesis, is a process where a nucleophile attacks an electron deficient center, forming a new bond and displacing a leaving group (Scheme 2.76). This can occur via either an  $\text{S}_{\text{N}}2$  mechanism, with bond making and bond breaking occurring at the same time or an  $\text{S}_{\text{N}}1$  mechanism with two steps and a planar carbenium ion intermediate.

### Scheme 2.76

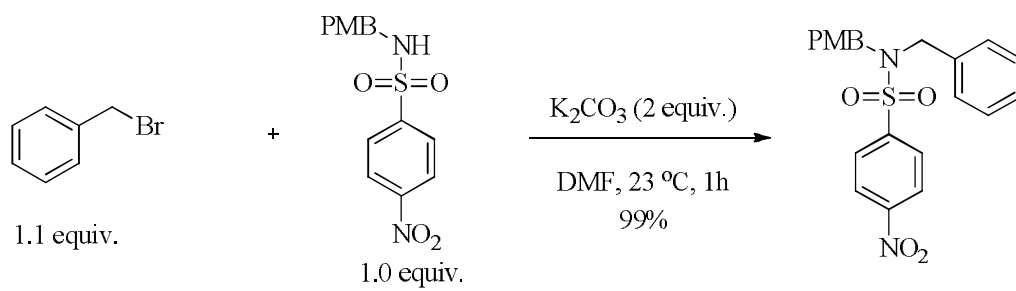


Addition of biologically relevant nucleophiles to an alkyl halide tether would allow for the introduction of a reactive functionality to an existing scaffold. Two such nucleophiles are morpholine and sulfonamides.<sup>171</sup> Addition of various morpholine analogues, including morpholine itself, to alkyl bromide substrates has been demonstrated by Berardi *et al.* (Scheme 2.77).<sup>172</sup> Sulfonamide addition has also been employed as demonstrated by Fukuyama *et al.* (Scheme 2.78).<sup>173</sup>

### Scheme 2.77



**Scheme 2.78**



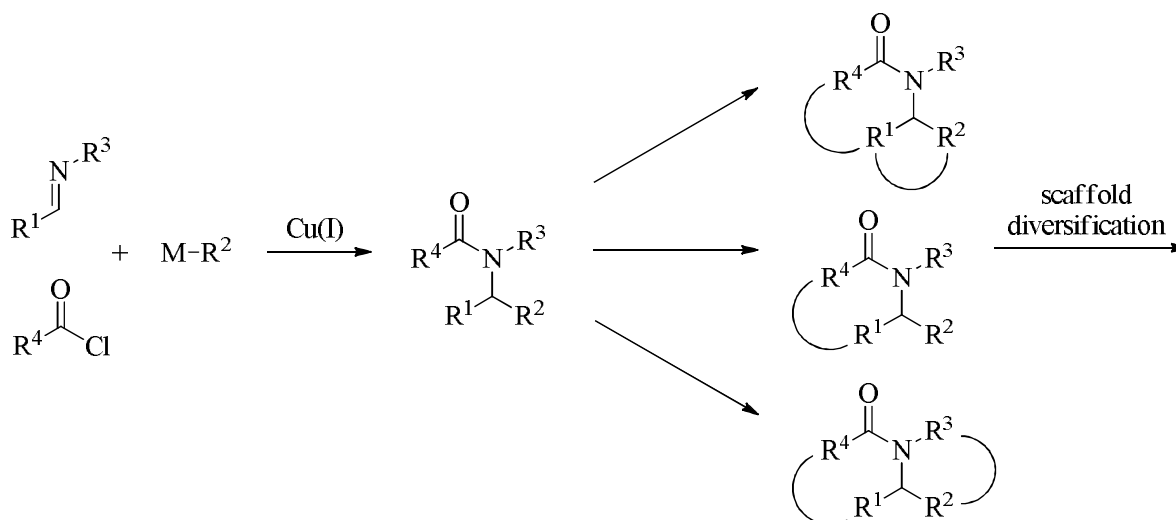
### **Chapter Three**

*Synthesis and Diversification of Aryl-Fused Azabicyclo[2.2.2]octanes via Cu/Pd/Ru Sequential  
Catalysis*



Diversity-oriented synthesis has emerged as an important aspect of modern organic chemistry.<sup>174</sup> In the Malinakova group we are interested in the sequencing of multicomponent reactions and subsequent annulation reactions in order to efficiently construct collections of functionally diverse molecular scaffolds (Scheme 3.1). More specifically, we wish to employ modified Arndtsen three-component coupling chemistry to synthesize carefully selected acyclic amide precursors which can then be cyclized into aryl-fused bridged *N*-heterocycles. For my first project I focused on the application of Heck cascade chemistry to polycyclic bridge formation in a single step.

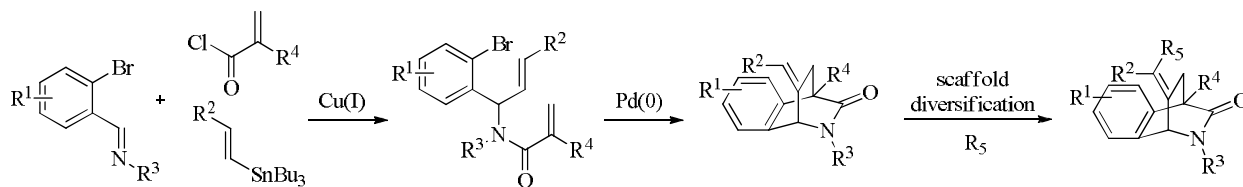
**Scheme 3.1**



The proposed Heck reaction would begin with oxidative addition of palladium across the aryl halide bond, followed by selective *syn* addition to one olefin and then the other.  $\beta$ -hydride elimination would then give a bridged product (Scheme 3.2). For the reaction to succeed and to achieve stereoselective *syn* addition it was important to carefully design the amide precursor. Once we had constructed the bridged scaffold we were then interested in exploring interesting avenues of diversification around that core structure. Although many diversification points were

explored, our primary focus was on allylic functionalization of the bridgehead olefin. This step proved to be the most challenging and therefore the most synthetically interesting.

### Scheme 3.2



This project attracted our attention for two reasons; first, although Arndtsen extensively explored the three-component process, very little has been done to develop the synthetic applications of his three-component coupling process. Secondly, our group hopes to expand on the observed lack of synthetic strategies for the formation of aryl-fused bicycloisoquinolines. We were also interested in expanding the current understanding of sequential organometallic diversity oriented synthesis.<sup>174</sup> The following chapter will outline our accomplishments thus far.

## 3.1 Cu-Catalyzed Three-Component Coupling

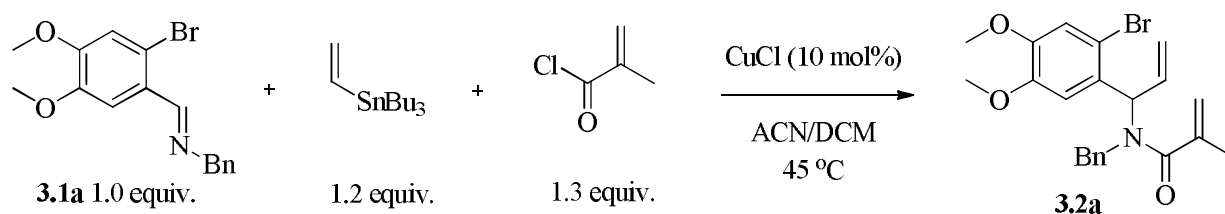
In order to explore a possible Heck cyclization we first needed to synthesize the desired amide precursor. We envisioned amide synthesis via a copper-catalyzed three-component coupling reaction between an imine, acid chloride and vinyl tin (Scheme 3.2). This process has been previously employed in our lab in the formation of indenoisoquinolines<sup>117</sup> and hexahydro-1*H*-isoindolones.<sup>118</sup>

### 3.1.1 Optimization of Conditions

Although the three-component coupling reaction has been previously optimized,<sup>113</sup> a number of modifications employed in my work have contributed to an improved yield of my specific amides. Modifications explored include addition of molecular sieves and changes in solvent ratio. In all cases CuCl, imine and acid chloride were pre-mixed in ACN for 20-30

minutes (at ambient temperature) to allow time for acyl iminium formation. A solution of vinyl tin in DCM was then added dropwise and the resulting solution was warmed to 45 °C and allowed to stir under argon for six hours. The mixture was then cooled to room temperature, quenched with aqueous KF, and stirred overnight. The crude product was then purified by column chromatography. It is important to note that the acyl iminium intermediate is highly susceptible to water hydrolysis.<sup>175</sup> For this reason all glassware was oven dried for at least six hours and only dry solvents were used. We also theorized that the addition of molecular sieves would suppress hydrolysis and thereby improve overall yield. This hypothesis stems from an earlier observation in our group where the addition of molecular sieves in the 3CC step had a positive effect on the yield.<sup>111a</sup> However, as can be seen when comparing entries 1 and 2 (Table 3.1), the addition of molecular sieves in my case greatly diminished the yield. We believe this problem arises due to the molecular sieves catalyzing a polymerization of the methacryloyl chloride.<sup>176</sup> We were also pleased to observe an increase in the yield when the polarity of the solvent system was decreased by increasing the proportion of DCM (entry 3, Table 3.1). Finally, comparable yields were observed when the reaction was run with imine loading ranging from 335 mg to 1.0 g indicating the reaction could be easily scaled up (entry 3 and 4, Table 3.1).

**Table 3.1**



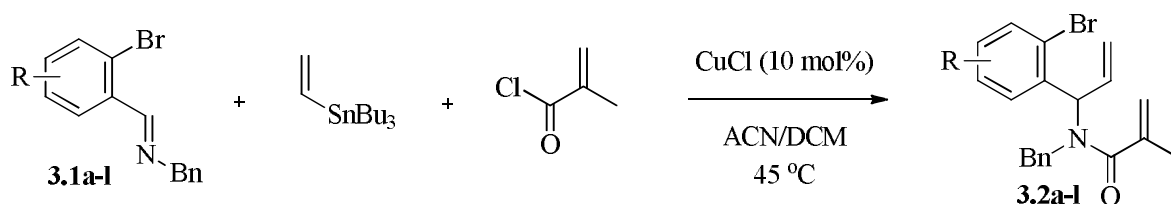
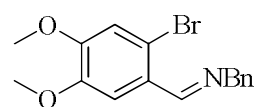
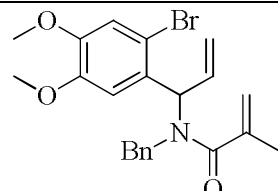
Entry	ACN : DCM	Amide <b>3.2a</b> (%) <sup>a</sup>
1 <sup>b</sup>	1.3 : 1.0	28
2	1.3 : 1.0	50
3	1.0 : 2.0	83 <sup>c</sup>
4	1.0 : 2.0	80 <sup>d</sup>

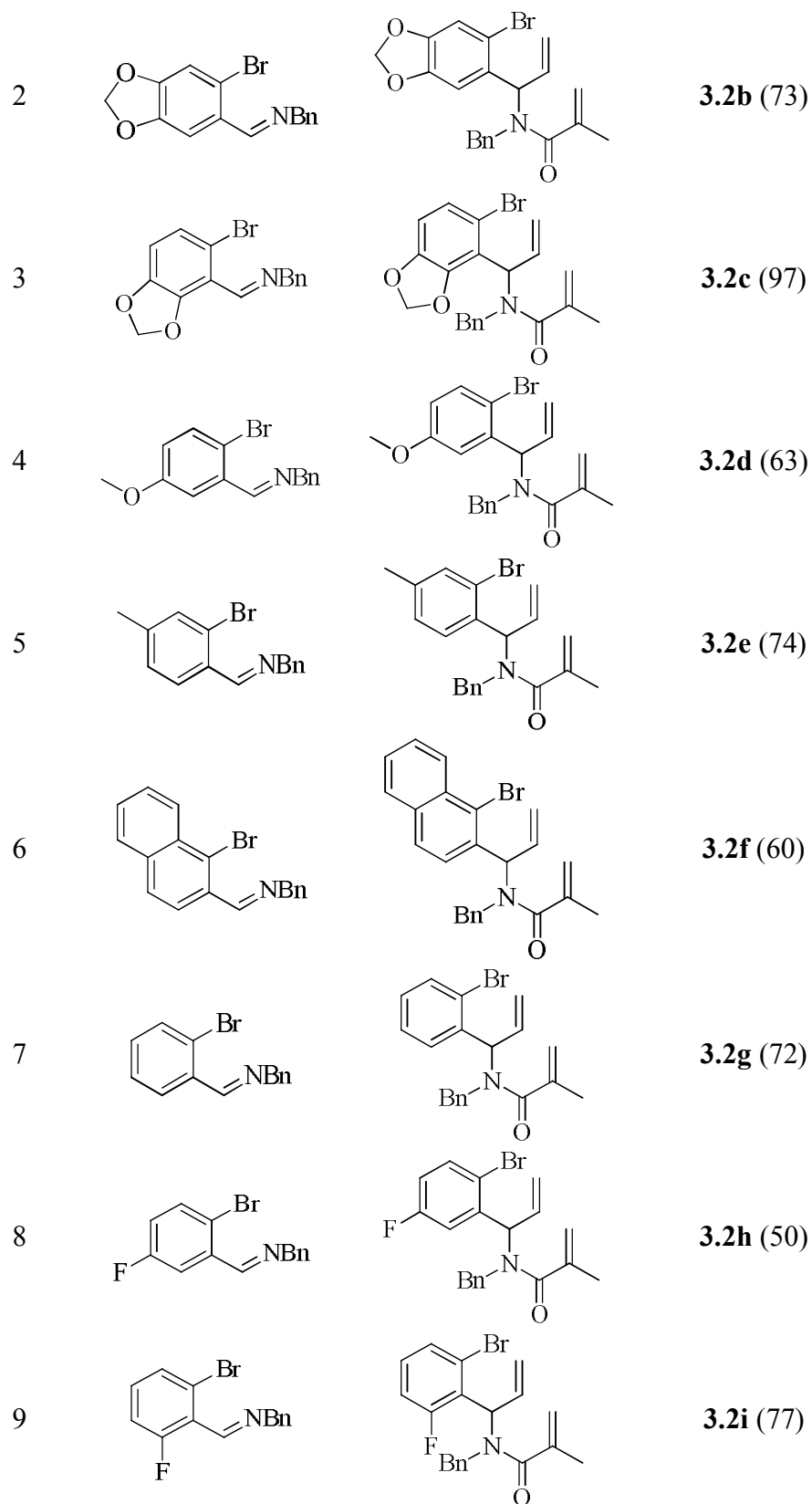
<sup>a</sup>Isolated yield of a single compound. <sup>b</sup>4Å molecular sieved added. <sup>c</sup>335 mg of imine used. <sup>d</sup>1.0 g of imine used

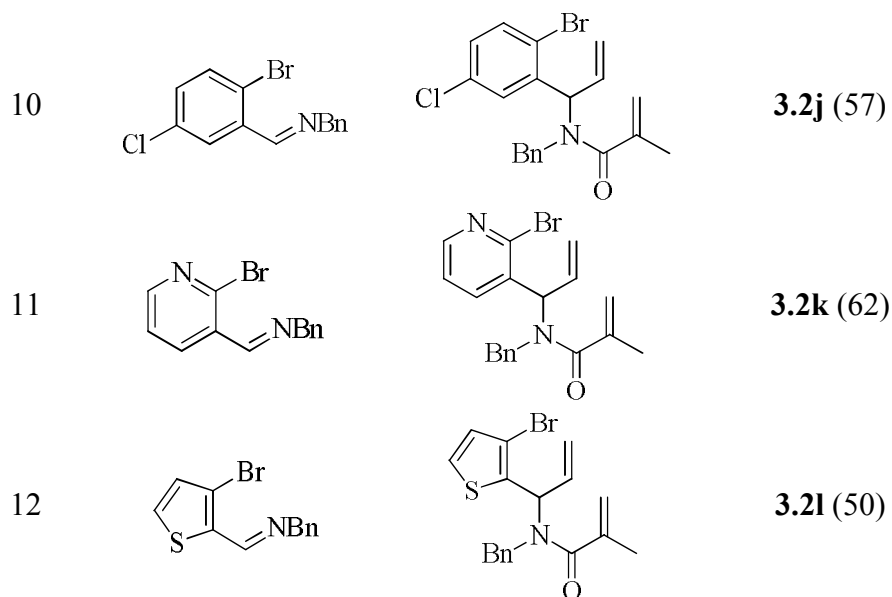
### 3.1.2 Variation of Aryl Imine

After the three-component coupling conditions were sufficiently optimized we then set out to synthesize a series of amide analogues. The first point of variation we chose to investigate was substitution in the aryl ring of the imine. As previously stated, there is a dearth of studies in the literature pertaining to structure-activity relationship of aryl-fused 2-azabicyclo[2.2.2]octanes. For this reason we felt that variation of the aryl-fused component would constitute a valuable synthetic contribution. As can be seen in Table 3.2, our improved protocol allowed for a successful installment of electronically diverse substituents to the aromatic ring, providing amides **3.2a-l** in good to moderate yields (Table 3.2). Significant signal broadening, arising due to hindered rotation about the amide C-N bond, was observed in <sup>1</sup>H and <sup>13</sup>C NMR spectra of the amides. Temperature dependent <sup>1</sup>H NMR spectra was collected for amide **3.2a** (Entry 1, Table 3.2) indicating that higher temperatures could reduce the occurrence of signal broadening.

**Table 3.2**

			
Entry	Imine 3.1	Amide 3.2	Amide 3.2 (%) <sup>a</sup>
3			<b>3.2a</b> (83)



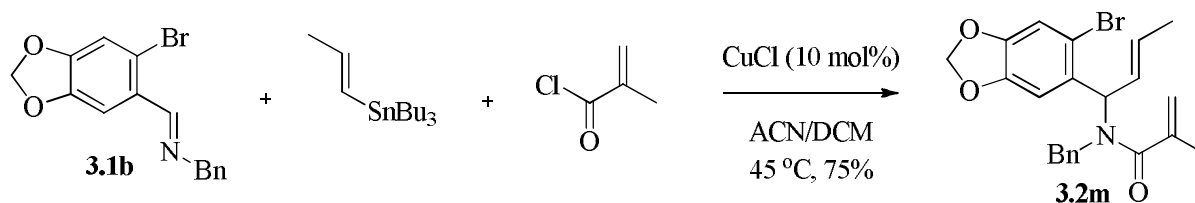


<sup>a</sup>Isolated yield of a single compound.

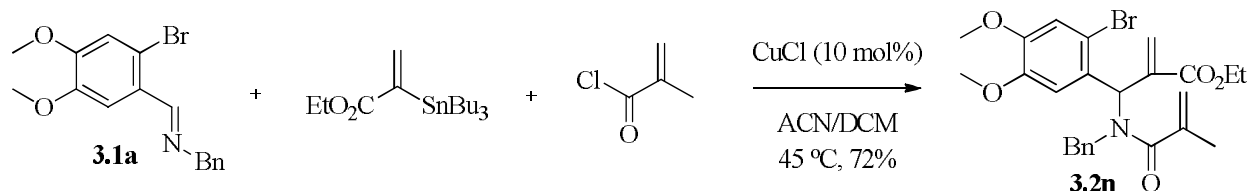
### 3.1.3 Variation of Vinyl Tin

In addition to diversification of the aryl imine component, we also explored variations in the structure of the vinyl tin and acid chloride. For the vinyl tin component we sought to determine the reactivity of both 1,2- and 1,1-disubstituted vinyl stannanes (Scheme 3.3). Three-component coupling was achieved using the previously optimized conditions using either commercially available tri-*N*-butyl(1-propenyl)stannane or ethyl 2-(tributylstannyl)acrylate, formed in a single step from commercially available ethyl propiolate and tributyltin hydride under previously established conditions.<sup>117</sup> The corresponding amides **3.2m** and **3.2n** were obtained in good yields, 75% and 72% respectively.

#### Scheme 3.3



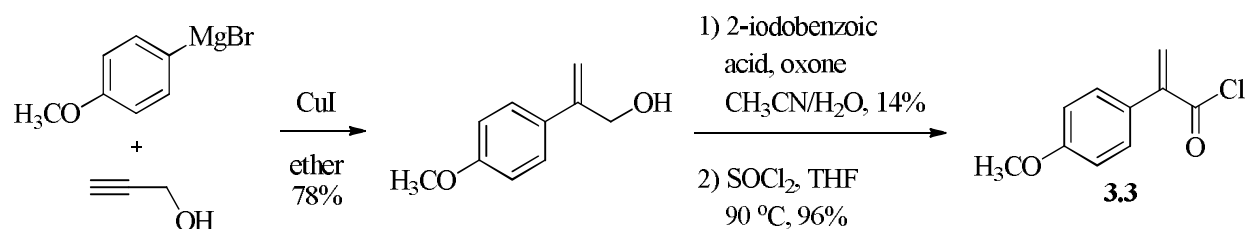
### Scheme 3.4



#### 3.1.4 Variation of Acid Chloride

The third variable we attempted to investigate was substitution in the C-2 position of the acroyl chloride. The first challenge of this process was to synthesize the C-2 substituted acroyl chloride. Nick Ruhs, a former undergraduate research student in our lab, took on this project to develop a method for synthesizing phenylacryloyl chloride **3.3** (Scheme 3.5). During his time in our lab Nick developed a three-step process including organocuprate addition, oxidation and chlorination to give the desired C-2 substituted acroyl chloride. Unfortunately, he was unable to improve the second step (14 % yield max) before his time with us ended and we were forced to abandon this project.

### Scheme 3.5

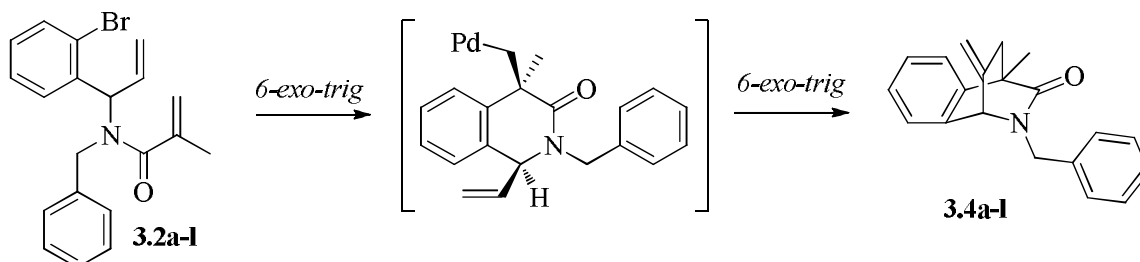


#### 3.2 Pd-Catalyzed Heck Cascade

As outlined in the previous chapter, the Heck reaction, specifically the intramolecular domino Heck cascade, has emerged as a power tool in modern synthetic organic chemistry for constructing complex heterocyclic scaffolds with novel carbon frameworks. Our proposal includes a two-fold Heck cascade process that would go through a *6-exo-trig* cyclization followed by another *6-exo-trig* cyclization to form bridged lactam **3.4** (Scheme 3.6). For this

transformation to be successful, the cyclization must proceed with a high regio- and stereoselectivity.

### Scheme 3.6

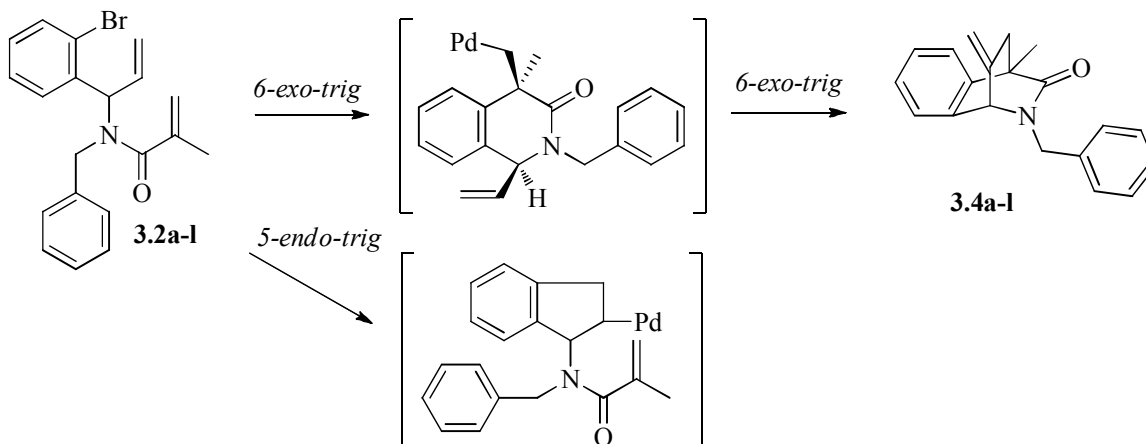


#### 3.2.1 Stereo- and Regioselectivity, Mechanism

Due to the presence of two olefins in the amide precursor, it is important to carefully consider which olefin will undergo carbopalladation first (Scheme 3.7). Once the palladium has inserted into the aryl bromide bond, carbopalladation may proceed through a *5-endo-trig* or *6-exo-trig* cyclization. According to Baldwin's rules<sup>69</sup> a *6-exo-trig* cyclization should be preferred over *5-endo-trig*. However, as demonstrated by Tanner *et al.* in 2006, under certain conditions the *5-endo-trig* pathway may be favored.<sup>71</sup> In spite of this precedent we still predicted a *6-exo-trig* cyclization to be the lower energy pathway because our substrate lacks unusual conformational restrictions. Presence of the methyl substituent in the acrylamide functionality is critical for preventing a premature termination of our cascade via  $\beta$ -hydride elimination.<sup>177</sup> Once the first *6-exo-trig* cyclization has occurred, we then predict a second *6-exo-trig* cyclization. However, for this to be possible, it is necessary for the palladium and mono-substituted olefin to be on the same face of the newly formed lactam ring. To determine if the palladium is expected to be on the same or opposite face we needed to consider the stereoselectivity of the cyclization.

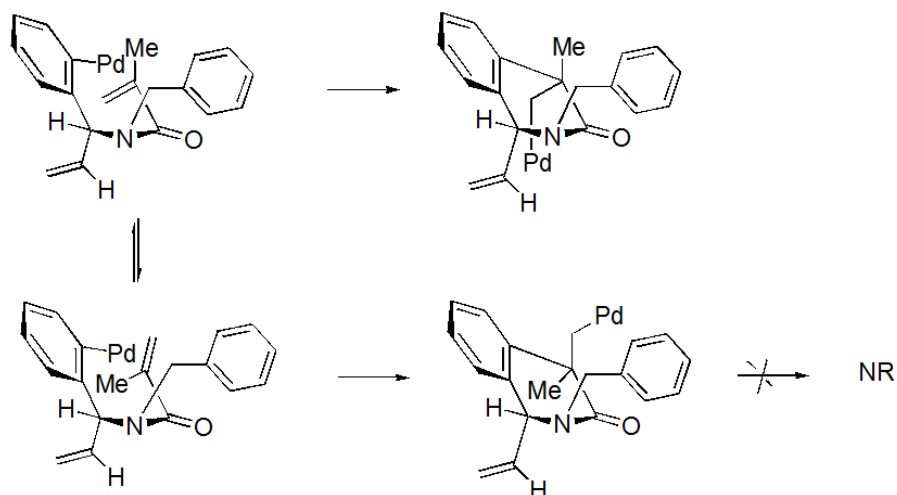
### Scheme 3.7





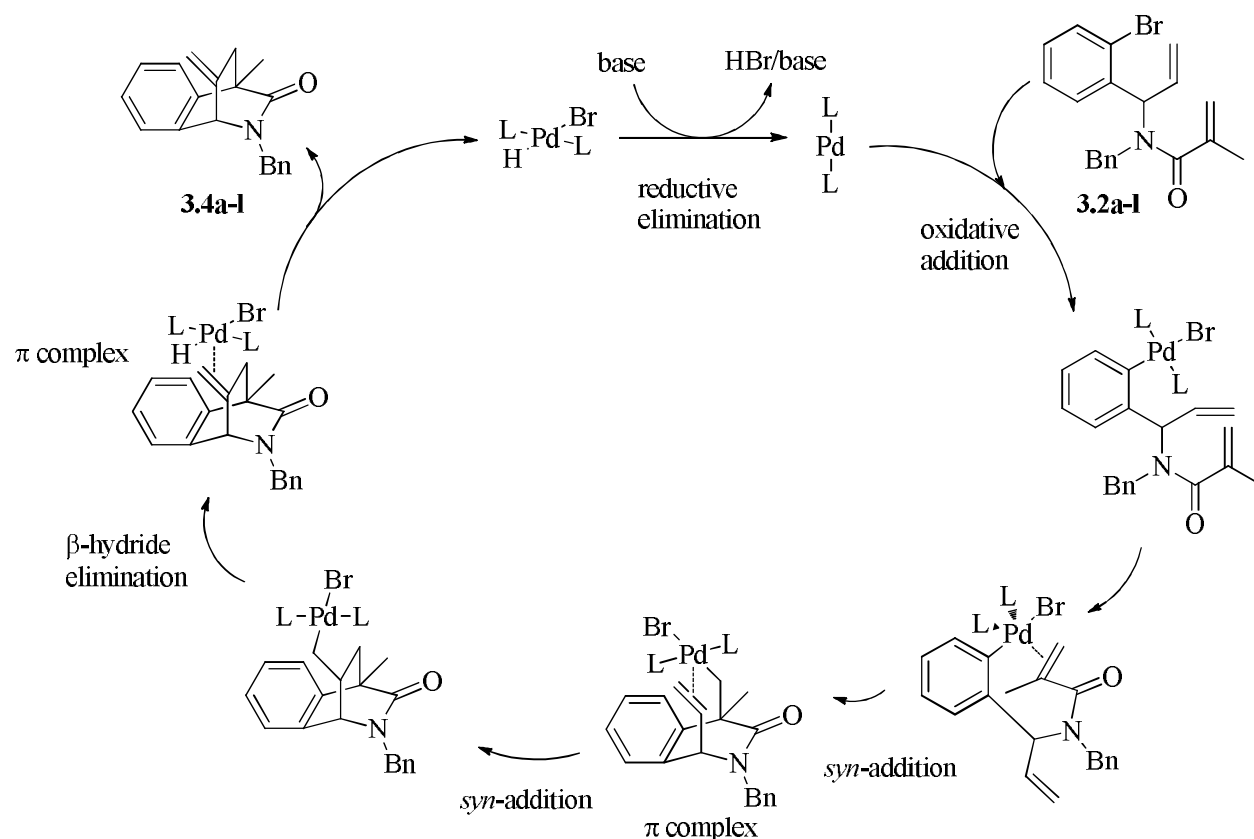
Once the palladium has undergone oxidative addition to the aryl halide, an equilibrium would exist between two conformations of the pre-cyclization amide intermediate (**I** and **II**), both having the mono-substituted olefin and *N*-benzyl protecting group in a low energy *anti* configuration (Scheme 3.8). The aryl palladium can then approach the 1,1-disubstituted olefin from one of two possible diastereotopic faces. Approach from the *re* face would lead to high energy intermediate **IV** with the palladium on the same face as the *N*-benzyl protection group. This would also result in the palladium being on the opposite face from the mono-substituted olefin thereby disallowing the second cyclization event. Alternatively, approach from the *si* face would produce intermediate **III** with the palladium and *N*-benzyl on opposite faces, thereby minimizing steric hinderance. In this case, the palladium would also be on the same face as the mono-substituted olefin allowing for the second cyclization to proceed. Thus, via the equilibrium between conformations **I** and **II**, all the substrate would be converted to desired intermediate **III**.

**Scheme 3.8**



The following catalytic cycle can be proposed for the assembly of the aryl-fused azabicyclo[2.2.2]octane core (Scheme 3.9). Oxidative addition would be followed by a two-fold *6-exo-trig* cyclization, and finally  $\beta$ -hydride elimination to give the bridged *N*-heterocyclic product. Reductive elimination, driven by the base, would then regenerate the palladium (0) catalyst. This strategy is superior to the benzyne Diels-Alder method of forming aryl-fused azabicyclo[2.2.2] octanes<sup>39</sup> because it allows for a wider variety of substituents to be attached to the aryl ring (Diels-Alder hindered by electronic requirements).

**Scheme 3.9**

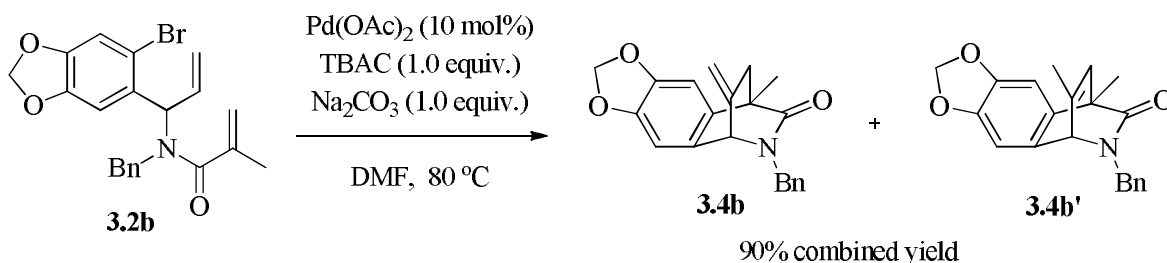


### 3.2.2 Proof of Concept

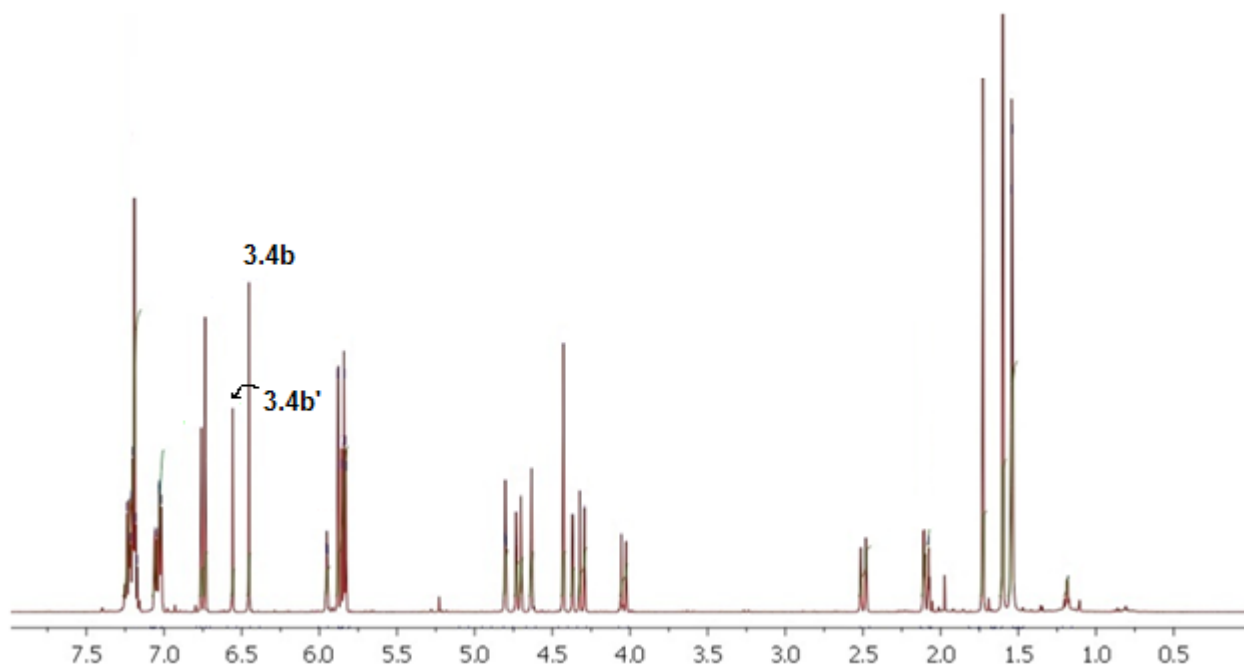
As a proof of concept for our proposed palladium-catalyzed Heck cascade, the reaction outlined in Scheme 3.10 was carried out. For our purposes we selected Jeffery's ligand less Heck conditions,<sup>67</sup> hypothesizing that cyclization would be improved by the olefins behaving as ligands for the palladium. A solution of amide **3.2a** (1.0 equiv.) in DMF (0.12 M) was injected into a vessel already containing the dry reagents including sodium carbonate (1.0 equiv.), tetrabutylammonium chloride (1.0 equiv.) and palladium acetate (10 mol%). The resulting yellow solution was stirred overnight at 80 °C then purified by column chromatography to give a 90% yield of the bridged product as a mixture of two isomers (**3.4a** and **3.4a'**) (Scheme 3.10). Although the yield was pleasingly high we were disappointed to observe that the two isomers were inseparable by column chromatography. The desired product was isolated as a mixture of

*exo* and *endo* isomers in a 1.5 : 1.0 ratio respectively (established by  $^1\text{H}$  NMR), with a combined yield of 90%.

**Scheme 3.10**



Fortunately, I was able to fully characterize the mixture using  $^1\text{H}$  NMR, establishing that we had isolated both the *exo* (**3.4b**) and *endo* (**3.4b'**) form of the product. Also, by comparing the integrations of the two signals at about 6.5 ppm, assigned to one of the protons on the substituted aromatic ring, I was able to determine the ratio of the *exo* and *endo* isomers at 1.5 : 1.0 respectively (Figure 3.1).



**Figure 3.1**  $^1\text{H}$  NMR of azabicyclooctane mixture of **3.4b** and **3.4b'**

### 3.2.3 Formation of Regioisomers

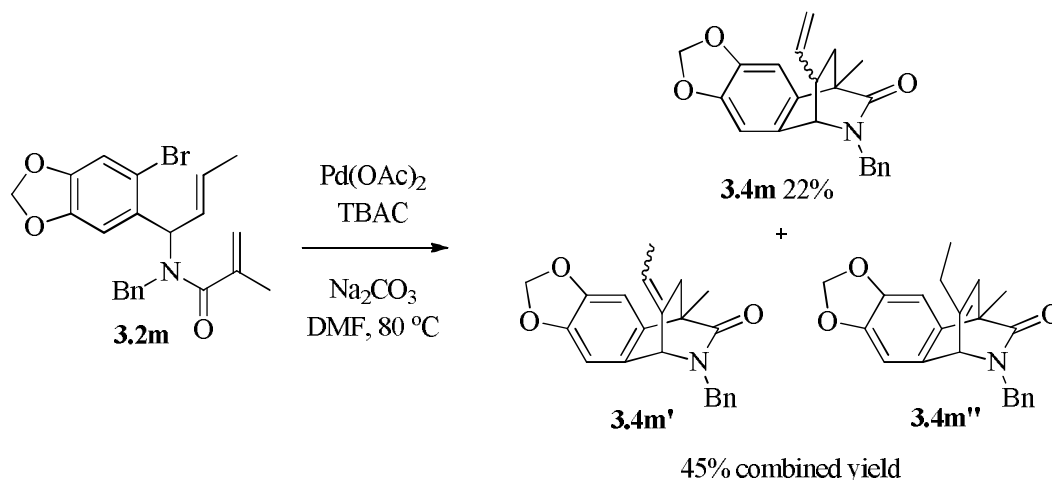
We propose that the formation of double bond isomer is due to readdition of the H-Pd(II)-(L)<sub>2</sub>Br species to the *exo* olefin, followed by an alternative β-hydride elimination to give the *endo* product (Scheme 3.11). Initial efforts to avoid isomer formation by variation of the base, with the intent of speeding up reductive elimination, resulted in only a slight change in the isomer ratio. Clearly a mixture of products was not desired; however as will be discussed shortly, we envisioned a novel methodology for transforming the isomer mixture into a single product via an additional scaffold diversification process. We have also eliminated the possibility to affect the ratio of the isomers via acid-catalyzed isomerization *vide infra*.

#### Scheme 3.11



isomer formation issue, the lack of selectivity was undesirable and so this transformation was not further explored.

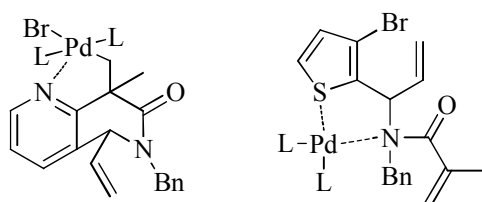
### Scheme 3.12



### 3.2.4 Synthesis of Analogues

As will be discussed in the next section, formation of an isomeric mixture was not foreseen to be a problem. For this reason, my next goal was to synthesize a library of these bridged *N*-heterocycles by varying the three-component coupling reagents. The first variable to explore was the aryl imine because it was evident from our review of the literature that the lack of aryl-fused azabicyclooctane analogues represented a significant gap in the literature. Using the previously synthesized amides (**3.2a-l**), I performed Heck cyclization with  $\text{Pd}(\text{OAc})_2$ , TBAC and  $\text{Na}_2\text{CO}_3$  in DMF at  $80^\circ\text{C}$  (Table 3.3). Heck cyclization of electron rich aryl amides **3.2a-d** produced an isomeric mixture of bridged products **3.4a-d** and **3.4a-d'** in good to excellent yields (Entries 1-4, Table 3.3). By comparison of entry 1 and 2 we were also able to observe a shift in isomer ratio when using a different regioisomer. Neutral aliphatic analogues **3.4e-g** and **3.4e-g'** were also obtained via Heck cyclization, which may prove significant for medicinal studies because they demonstrate variation in shape of the hydrophobic region (Entry 5-7, Table 3.3).

Heck cyclization of electron deficient aryl halides was also successful, affording regioisomer mixtures **3.4h-j** and **3.4h-j'** (Entry 8-10, Table 3.3). Finally we explored the use of heteroaryl amides. Unfortunately, using electron deficient pyridine **3.2k**, we did not observe formation of azabicyclooctane **3.4k** (Entry 11, Table 3.3) and electron rich thiophene **3.2l** afforded a low 12% yield of azabicyclooctane **3.4l**, as a single regioisomer. Our hypothesis is that the heteroaryl analogues hinder the success of the reaction through chelation with the palladium catalyst (Figure 3.2).

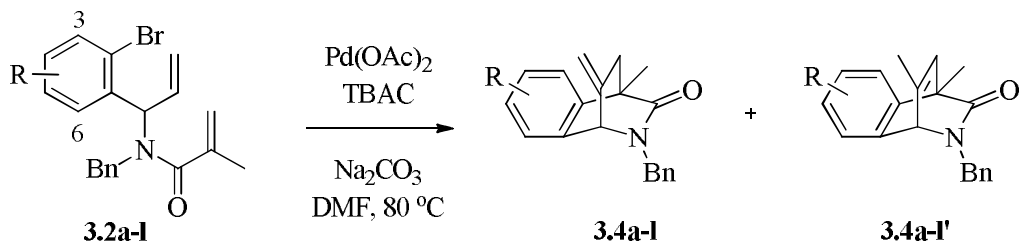


**Figure 3.2.** Possible chelation in heteroaryl cyclization intermediates.

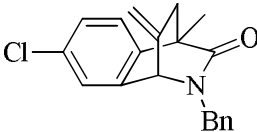
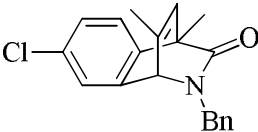
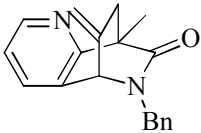
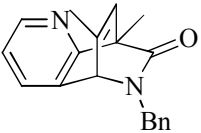
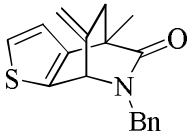
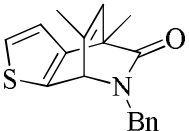
Interestingly, cyclization of bulky naphthyl amide **3.2f**, substituted at the 3 position, afforded the greatest product ratio, with a significant excess of the *exo* isomer (Entry 6, Table 3.3). Conversely, amides **3.2c** and **3.2i**, both substituted at the 6 position, afforded the azabicyclo octane product with an excess of the *endo* isomer (Entry 3 and 9, Table 3.3). Additional analogues would need to be synthesized to fully understand this interesting observation. Another interesting observation is the fluorinated bicyclooctanes **3.4i** and **3.4i'** were separable by column chromatography (Entry 9, Table 3.3). With these results, we can conclude that the electronic properties of substituents on the aryl functionality have no significant effect on the success of the Heck cyclization, however steric- and electronic properties both appear to affect the isomer ratio.

**Table 3.3**





Entry	Amide <b>3.2</b>	Bicyclooctanes <b>3.4</b>		Bicyclooctanes <b>3.4 (%)</b> <sup>a</sup>	<b>3.4 : 3.4'</b> <sup>b</sup> (%)
1	<b>3.2a</b>			<b>3.4a : 3.4a'</b> (68)	57 : 43
2	<b>3.2b</b>			<b>3.4b : 3.4b'</b> (90)	60 : 40
3	<b>3.2c</b>			<b>3.4c : 3.4c'</b> (80)	33 : 67
4	<b>3.2d</b>			<b>3.4d : 3.4d'</b> (65)	57 : 43
5	<b>3.2e</b>			<b>3.4e : 3.4e'</b> (77)	1.1 : 1.0
6	<b>3.2f</b>			<b>3.4f : 3.4f'</b> (65)	52 : 48
7	<b>3.2g</b>			<b>3.4g : 3.4g'</b> (89)	50 : 50
8	<b>3.2h</b>			<b>3.4h : 3.4h'</b> (66)	55 : 45
9	<b>3.2i</b>			<b>3.4i : 3.4i'</b> (93) <sup>c</sup>	42 : 58

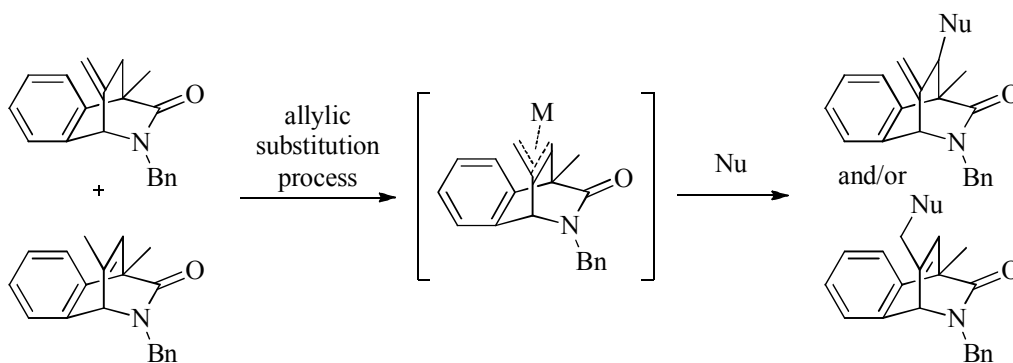
10	<b>3.2j</b>			<b>3.4j : 3.4j'</b> (80)	52 : 48
11	<b>3.2k</b>			<b>3.4k : 3.4k'</b> (0)	-
12	<b>3.2l</b>			<b>3.4l : 3.4l'</b> (12) <sup>d</sup>	100 : 0

<sup>a</sup>Combined isolated yield of an inseparable mixture of two regioisomers. <sup>b</sup>Molar ratio of the regioisomers established by <sup>1</sup>H NMR. <sup>c</sup>Combined yield of two regioisomers separated by column chromatography. <sup>d</sup>Isolated yield of a single compound

### 3.3 Reactions with the Bridgehead Olefin in the Regioisomer Mixture

As previously stated, we did not foresee the isomer mixture to be a problem, but rather a challenging synthetic obstacle. To resolve the isomer mixture we hypothesized taking the two isomers through a common intermediate ( $\pi$  allyl or resonance stabilized radical) via an allylic substitution reaction (scheme 3.13). Selective nucleophilic addition to this common intermediate could then produce a single product. As it turns out “challenging” is an understatement.

#### Scheme 3.13

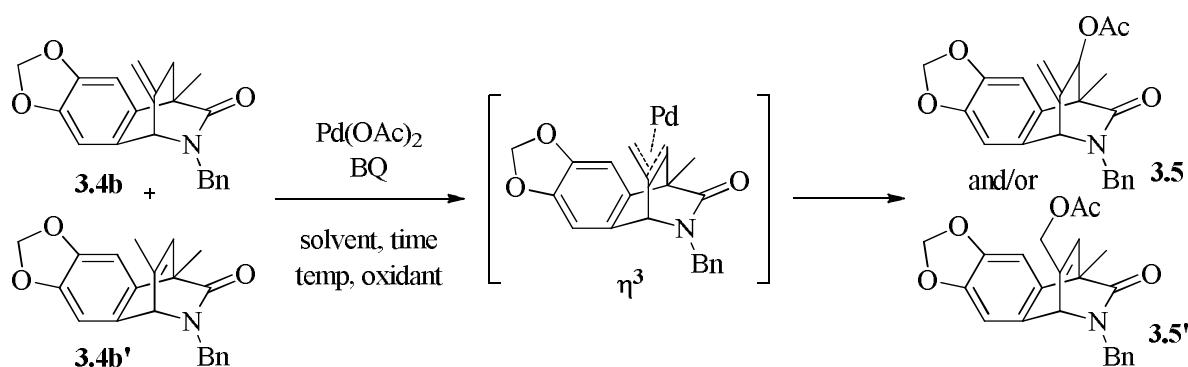


#### 3.3.1 Acetoxylation

Transition metal catalysis is not only of major interest to modern organic chemistry but it is also of central interest to the Malinakova group. For this reason, we chose to begin our

exploration of allylic functionalization with the palladium-catalyzed acetoxylation method with the intent of taking our two isomers through a common  $\pi$  allyl intermediate (Scheme 3.14). This method was also attractive to us because, in spite of the relatively large amount of research towards the development of this method, little has been done in regard to acetoxylation of more complex sterically congested scaffolds.

**Scheme 3.14**



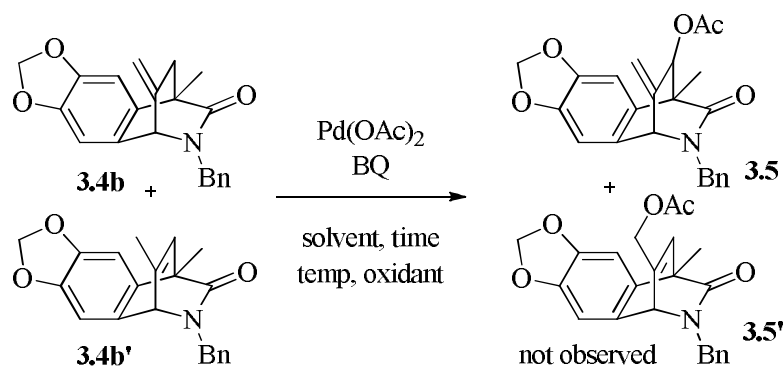
As a proof of concept we first decided to try Christina White's conditions.<sup>139</sup> A solution of the isomer mixture (1.0 equiv.) in DMSO (0.23M) was added to an open flask already containing the solid reagents Pd(OAc)<sub>2</sub> (0.1 equiv.) and benzoquinone (2.0 equiv.). Acetic acid (0.23 M) was then added, the flask was sealed and the resulting solutions stirred at 40 °C. Unfortunately, TLC monitoring continued to indicate the presence of starting material only. After 72 hours the reaction was quenched with ammonium chloride and purified by column chromatography affording an 88% recovery of starting material and no acetoxylated product (Entry 1, Table 3.4). Initially we hypothesized that the reaction failed due to poor introduction of the air oxidant; however, when the reaction was run again, this time with air being bubbled through the solution just prior to sealing, the reaction failed once again (Entry 2, Table 3.4). Although attractive as an oxidant, our theory is that air is not an effective oxidant in our system. For this reason we choose to move on to alternative oxidants. Changing the oxidant to one

atmosphere of oxygen (Entry 3, Table 3.4) we were pleased to obtain a 12% yield of acetoxylated product **3.5** (86% recovery of starting material). This result, although low yielding, proved to us that acetoxylation of the isomer mixture was indeed possible. In addition, further analysis of the product revealed that a single regio- and stereoisomer was produced indicating that selective addition of the acetate anion into the  $\pi$  allyl intermediate was achieved. Thinking that other oxidants may further improve the yield, we next tested Akermark conditions, which utilized hydrogen peroxide.<sup>141a</sup> A flask was charged with the isomer mixture (1.0 equiv.) Pd(OAc)<sub>2</sub> (0.05 equiv.) and BQ (0.1 equiv.) followed by addition of acetic acid (0.2 M) and H<sub>2</sub>O<sub>2</sub>. The yellow solution was then stirred at 50 °C under argon. After two days, TLC monitoring indicated presence of starting material and a new spot. Subsequent purification gave us an 18% yield of the same acetoxylated product, along with 45% recovery of starting material (Entry 4, Table 3.4). The yield was further improved to 30% by increasing the reaction temperature from 50 °C to 75 °C (Entry 5, Table 3.4). Unfortunately, this is where the success story ended. Over the next several months various reactions conditions were tested with the yield never rising above 30%.

Continuing with variations in the oxidant, I next tried TBHP<sup>141a</sup> and manganese dioxide,<sup>142</sup> both resulting in a diminished yield (Entry 5-6, Table 3.4). After identifying hydrogen peroxide as the best oxidant, I then moved on to investigate other variables. Our next hypothesis was that our Pd(OAc)<sub>2</sub> and BQ samples were old and recrystallization should improve the yield. However, use of recrystallized Pd(OAc)<sub>2</sub> resulted in a diminished yield (Entry 7-9, Table 3.4). Addition of recrystallized benzoquinone also failed to improve product formation (Entry 10, Table 3.4). Considering these results, we decided that perhaps it was not the quality of the catalyst, but rather the loading that was affecting yield. Our theory was that the palladium catalyst was not achieving the proper number of turnovers in the catalytic cycle and addition of

excess catalyst should restart the reaction. To test this we ran the synthesis with excess catalyst at the start (Entry 11, Table 3.4), addition of excess catalyst in three installments 4 hours apart (Entry 12, Table 3.4) and a stoichiometric amount of catalyst (Entry 13, Table 3.4).<sup>147c</sup> Unfortunately, this too failed to improve the yield. Changing the solvent system<sup>148</sup> (Entry 14-15, Table 3.4) and catalyst<sup>141a</sup> (Entry 16, Table 3.4) also proved unsuccessful in improving yield. In spite of the low yield, we were pleased to observe formation of the desired acetoxylated product in all but two entries as a single diastereomer.

**Table 3.4**



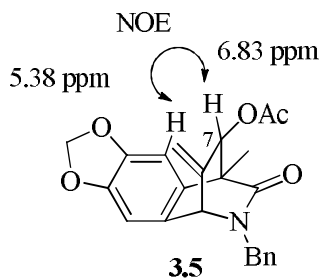
Entry	Pd(OAc) <sub>2</sub> (%)	BQ (equiv.)	Solvent	Time (h)	Temp (°C)	Oxidant (equiv.)	3.5 (%) <sup>a</sup>	3.4 (%) <sup>b</sup>
1	10	2	DMSO/ AcOH	72	40	air	0	88
2 <sup>c</sup>	10	2	DMSO/ AcOH	44	40	air	0	69
3	10 <sup>d</sup>	1.9 <sup>d</sup>	DMSO/ AcOH	47	40	O <sub>2</sub> (1 atm)	12	86
4	5	10	AcOH	44	50	H <sub>2</sub> O <sub>2</sub> (3.8)	18	45
5	5	0.1	AcOH	43.5	75	H <sub>2</sub> O <sub>2</sub> (4.1)	30	38
6	5	0.1	AcOH	52	75	TBHP (1.7)	14	31
7	5 <sup>d</sup>	0.2	AcOH	49	50	MnO <sub>2</sub> (2.0)	14	66
8	5 <sup>d</sup>	0.1	AcOH	47	75	H <sub>2</sub> O <sub>2</sub> (4.1)	21	40
9	5 <sup>d</sup>	0.1	AcOH	26	80	H <sub>2</sub> O <sub>2</sub>	25	38

						(3.0)		
10	5 <sup>d</sup>	0.1 <sup>d</sup>	AcOH	24	60	H <sub>2</sub> O <sub>2</sub> (1.5)	20	56
11	30	0.2	AcOH	21	75	H <sub>2</sub> O <sub>2</sub> (16.5)	17	40
12	15 <sup>e</sup>	0.1	AcOH	23	40	H <sub>2</sub> O <sub>2</sub> (3.7)	20	37
13	100 <sup>d</sup>	2	AcOH	27.5	80	H <sub>2</sub> O <sub>2</sub> (3.0)	25	5
14	10	0.2	DMSO/ AcOH	22	75	H <sub>2</sub> O <sub>2</sub> (16.5)	12	30
15 <sup>f</sup>	10	2	AcOH/ dioxane	48	43	-	12	79
16	5 Pd(OTFA) <sub>3</sub>	0.1	DCM/ AcOH	21	80	H <sub>2</sub> O <sub>2</sub> (3.0)	10	83

<sup>a</sup>Isolated yield of a single compound. <sup>b</sup>Combined isolated yield of an inseparable mixture of two regioisomers. <sup>c</sup>Run in a sealed pressure tube after air bubbling for 2 minutes. <sup>d</sup>Recrystallized.

<sup>e</sup>Three sequential additions of catalyst, 5% each four hours apart. <sup>f</sup>With (vinylsulfinyl)benzene.

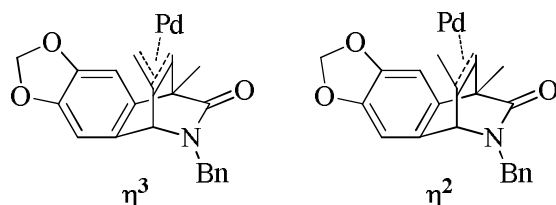
Using <sup>1</sup>H NMR NOE analysis, the stereochemistry at the C-7 center was shown to possess an *R* configuration (Figure 3.3). Irradiation of the allylic proton at 5.38 ppm caused an enhancement in the aromatic proton at 6.83 ppm.



**Figure 3.3** <sup>1</sup>H NMR NOE of acetate 3.5

To rationalize the low yield observed in Table 3.4 we need to first consider the mechanism of acetoxylation. For acetoxylation to be successful, the substrate must be able to orient itself in such a way that an allylic H can be removed to form a  $\pi$  allyl intermediate. In our case, we believe that due to rigidity and ring strain in the bridged system, the substrate cannot assume the proper conformation and/or the resulting  $\pi$  allyl intermediate is too high in energy

(Figure 3.4). Another possibility is that, if the substrate is truly unable to properly orient an allylic H, the reaction may be going through a Wacker type  $\eta^2$  intermediate. However, this seems unlikely due to the recovered starting material having the same double bond isomer ratio. At this point we remain unsure as to why the reaction is so low yielding.

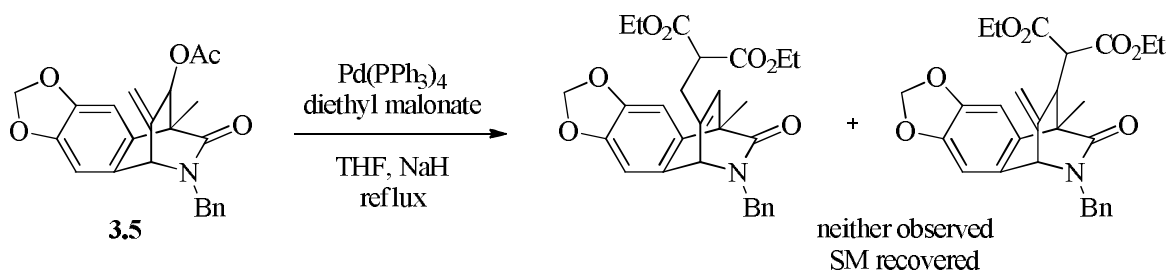


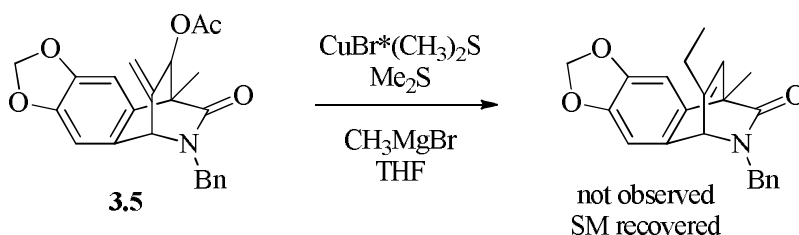
**Figure 3.4** Possible  $\pi$ -allyl intermediates

### 3.3.2 Tsuji-Trost and Organocuprate Substitution

While continuing to explore improvement of the acetoxylation results, we moved on to test Tsuji-Trost and organocuprate substitution of the acetoxylation product (Scheme 3.15). However, in both cases we failed to obtain the substituted product with both reactions resulting in starting material recovery. Once again, we ascribe reaction failure to stereoconformational constraints, causing the  $\pi$  allyl intermediate to be too high in energy for the Tsuji-Trost and steric constraints hindering the cuprate addition (note:  $R_2Cu$  would not require  $\pi$  allyl necessarily).

**Scheme 3.15**

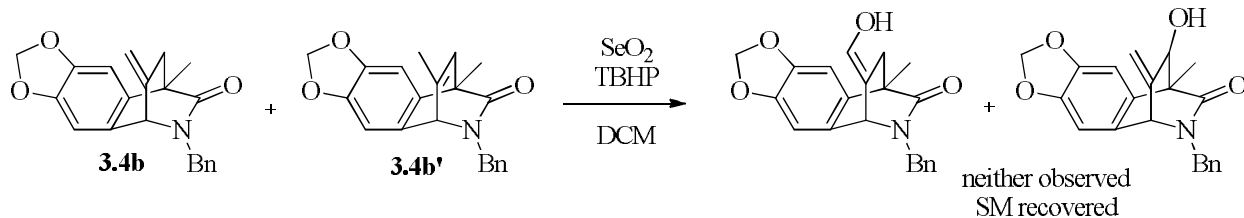




### 3.3.3 Selenium Dioxide Oxidation

Although an attractive modern methodology, palladium-catalyzed allylic substitution of our bridged structure had proven ineffective. Our next effort was to explore alternative allylic substitution pathways. First we tried selenium dioxide mediated oxidation (with tetrabutyl hydrogen peroxide and DCM) intending to form an alcohol product via a pericyclic process (Scheme 3.16). Unfortunately, oxidation of our isomer mixture failed to give the desired product (starting material recovered).

**Scheme 3.16**

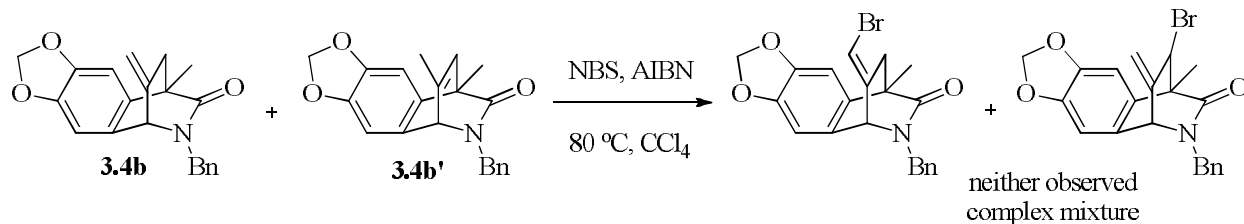


### 3.3.4 Allylic Bromination

Next we tried allylic bromination using *N*-bromosuccinimide (NBS) and AIBN (radical initiator) in carbon tetrachloride (at 80 °C) (Scheme 3.17). Once again we failed to observe product formation; however, this time a complex mixture rather than starting material was recovered. Our theory is that the high energy strained radical intermediate is rearranging into a less strained (non-bridged) form.<sup>178</sup>

**Scheme 3.17**

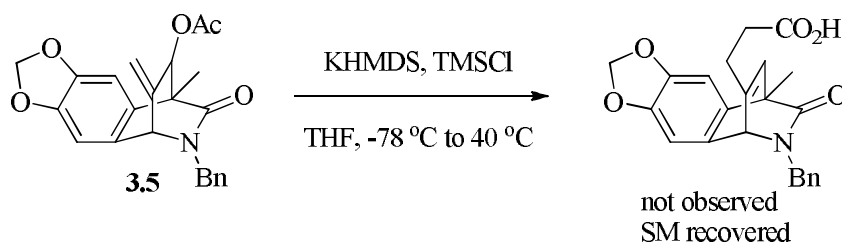




### 3.3.5 Ireland-Claisen Rearrangement

To test the hypothesis of conformational restriction we next tried an Ireland-Claisen rearrangement on allyl acetate **3.5** (Scheme 3.18). This reaction takes advantage of a base-catalyzed enolate formation, followed by a Claisen-like rearrangement, to afford the chain extended product terminated by a carboxylic acid. However, rather than obtaining the desired carboxylic acid product, the starting material was recovered, providing additional support to our conformational restriction hypothesis.

**Scheme 3.18**



### Summary of Allylic Functionalization

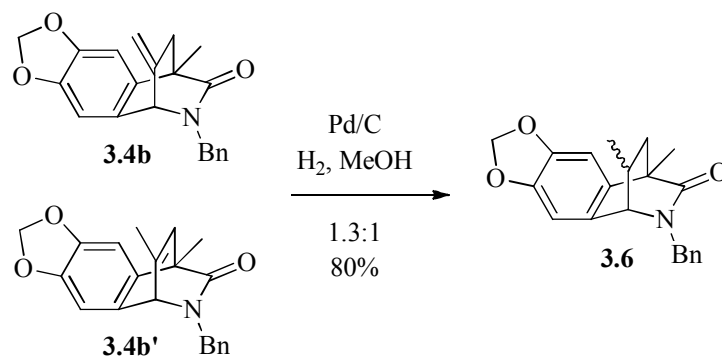
In summary, to our great disappointment, allylic substitution of our isomer mixture was not possible; acetoxylation alone afforded a low yield of the desired product. These results demonstrated an important fundamental reality in organic synthesis. In spite of our extensive understanding of a reaction, including mechanism, electronic and steric requirements, and ability to predict the outcome, when applied to a specific complex structure, nothing is certain. Allylic functionalization of our complex, sterically congested and rigid bridged *N*-heterocyclic structure proved a far greater challenge than reactions with relatively simple and flexible substrates

reported in the literature. Although the desired outcome was not achieved, this series of experiments has led us to an in-depth understanding of the chemical nature of our compound.

### 3.3.6 Catalytic Hydrogenation

In addition to the previously described allylic functionalization methods we also endeavored to convert the mixture of regioisomers into a single diastereomer via stereoselective catalytic hydrogenation. For our initial test we tried hydrogenation with H<sub>2</sub> (g) and palladium on carbon catalyst (Scheme 3.19). A solution of the isomeric mixture (1.0 equiv.) in methanol (0.03M) was injected into a flask containing palladium on carbon (10 mol%) and the resulting mixture was stirred overnight with H<sub>2</sub> continuously bubbling through the solution. After purification, we obtained an inseparable mixture of two diastereomers (**3.6**) in a 1.3:1 ratio (established by <sup>1</sup>H NMR) in an 80% combined yield. Although this did indicate a slight degree of selectivity, we were unable to obtain a single diastereomer.

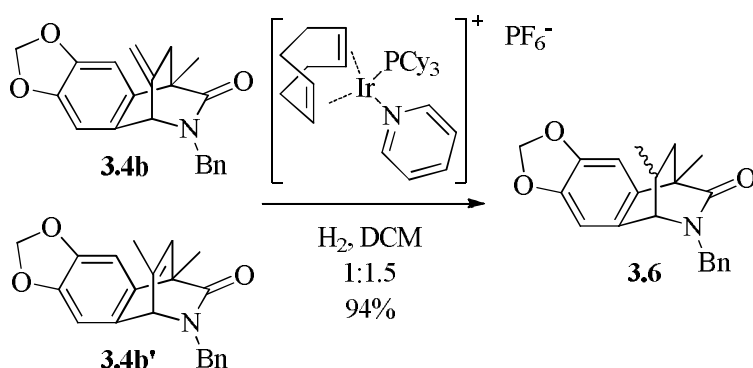
**Scheme 3.19**



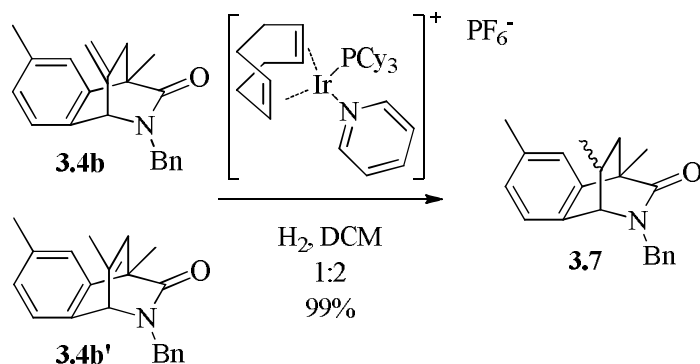
In order to improve selectivity the reaction was run again, this time exchanging the palladium on carbon catalyst for a chelation-controlled selective reducing agent (i.e. Crabtree's catalyst) (Scheme 3.20). Once again, we failed to observe a completely stereoselective reduction, affording a diastereomeric mixture of lactam **3.6**; however, in this case the selectivity was inverted as would be expected. We theorized that the selectivity was incomplete due to the

presence of chelating oxygens and nitrogens on both sides of the olefin. For this reason, we ran the reduction a third time, this time using alternative substrate mixture **3.4b** and **3.4b'**, affording a diastereomeric mixture of lactam **3.7**, for which selectivity was slightly improved but still far from complete (Scheme 3.21). We can speculate that, due to chelation with the amide carbonyl, the catalyst would preferentially approach from that side of the olefin; however, additional studies are needed to assign the relative stereochemistry for the major and minor isomers. Due to the observed limited stereoselectivity, and our inability to separate the two distereomers, we move on to explore alternative strategies for conversion of the mixture to a single product.

**Scheme 3.20**



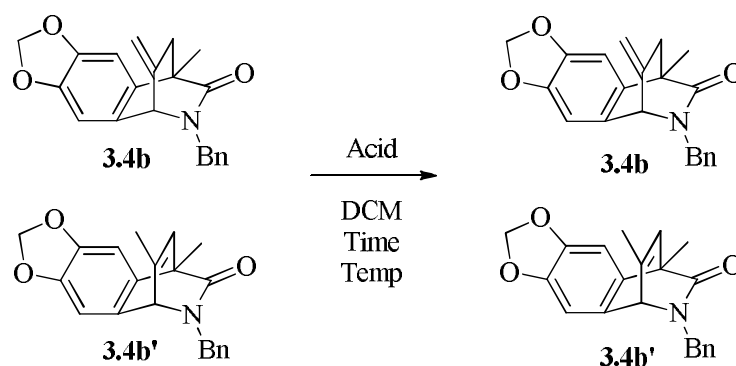
**Scheme 3.21**



### 3.3.7 Acid-Catalyzed Isomerization

Acid-catalyzed isomerization was also attempted on the mixture *vide supra* (Table 3.5). The theory here was that, although the *exo* isomer was major, under acidic conditions the *exo* olefin would isomerize into the more stable *endo* form. With this in mind, a series of experiments were run using either sulfuric acid or tosylic acid (Table 3.5). Initially, we were pleased to see a promising shift in the regioisomer ratio when the reaction was run with sulfuric acid at 25 °C for 19 hours (Entry 1, Table 3.5). However, by <sup>1</sup>H NMR analysis, we observed that we had not achieved complete conversion to the *endo* product. We next tried the reaction at an elevated temperature (50 °C) for a comparable amount of time and were surprised to obtain the same product regioisomer ratio (Entry 2, Table 3.5). Transitioning to tosylic acid we observed the same product ratio running the reaction at both 25 °C for four hours and 50 °C for 17.5 hours (Entry 3-4, Table 3.5). From these results we can conclude that a thermodynamic equilibrium between the two regioisomers has been reached.

**Table 3.5**



Chemical reaction scheme showing the acid-catalyzed isomerization of a mixture of **3.4b** and **3.4b'** to a mixture of **3.4b** and **3.4b'**. The reaction is catalyzed by Acid in DCM over Time at Temp.

Entry	Acid	Temp (°C)	Time (h)	SM <i>Exo</i> : <i>Endo</i> (%) <sup>a</sup>	Pdt <i>Exo</i> : <i>Endo</i> (%) <sup>a</sup>
1	H <sub>2</sub> SO <sub>4</sub>	25	19	60 : 40	33 : 67
2	H <sub>2</sub> SO <sub>4</sub>	50	17.5	60 : 40	33 : 67
3	TsOH	25	4	60 : 40	33 : 67

4	TsOH	50	17.5	60 : 40	33 : 67
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<sup>a</sup>Mole ratio of the regioisomers established by <sup>1</sup>H NMR.

In summary, diversification of the bridged *N*-heterocycle olefin isomer mixture has proven to be extremely challenging and largely unsuccessful. Acetoxylation of the mixture afforded a modest 30% yield of **3.5** as a single diastereomer; however we were unable to improve that yield, or perform substitution on the acetoxyated product. Other methods of allylic substitution also failed to produce the desired effect, namely selenium dioxide oxidation, allylic bromination and Ireland-Claisen rearrangement. In addition, efforts to selectively reduce the olefin mixture or to isomerize the mixture into a single product also failed. Although this would have been a powerful method of transforming the isomer mixture arising from the Heck reaction, we clearly needed to rethink our strategy.

### 3.4 Return to Pd-Catalyzed Heck Cascade

Although conversion of the olefin isomer mixture would have represented an interesting contribution to organic synthesis, extensive investigation of potential methods and their subsequent failure has forced us to abandon this possibility. For that reason, we next decided to return to the Heck cyclization conditions and endeavor to synthesize a single product. We propose to achieve single isomer formation by either changing the conditions, or via trapping of the aryl-palladium intermediate just prior to  $\beta$ -hydride elimination. Trapping methods that we investigated include carbonylation,<sup>96</sup> reductive Heck termination<sup>93</sup> and Suzuki termination with a boronic acid.<sup>98</sup>

#### 3.4.1 Trapping Reactions

Reductive Heck termination was attempted on amide **3.2b** using Jeffery's ligandless Heck conditions (Scheme 3.22).<sup>67</sup> We had expected to get a mixture of diastereomers, however the crude product was far more complex and we were unfortunately unable to clearly discern the

outcome. Similar inconclusive results were obtained when I performed a reductive Heck cyclization on amide **3.2n**, using either Jeffery's ligandless Heck conditions (Entry 1-2, Table 3.6)<sup>67</sup> or standard reductive Heck conditions (Entry 3-4, Table 3.6).<sup>93b</sup>

### Scheme 3.22

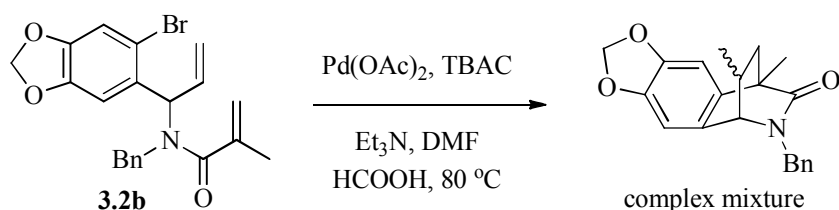
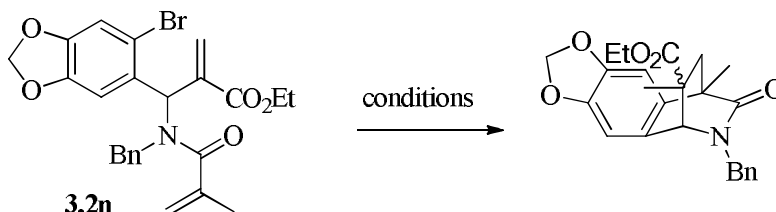


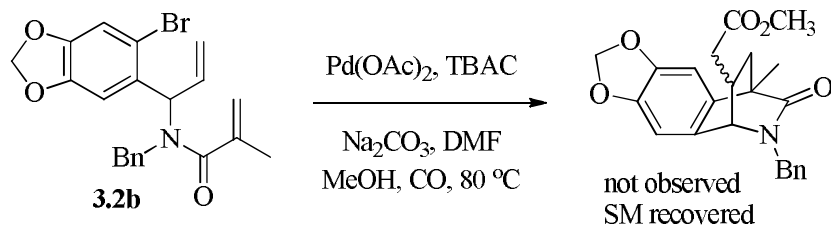
Table 3.6



Entry	Conditions	Outcome
1	$\text{Pd}(\text{OAc})_2$ , TBAC, $\text{Na}_2\text{CO}_3$ , $\text{Et}_3\text{N}$ , $\text{HCOOH}$ , DMF, $80\text{ }^\circ\text{C}$	complex mixture
2	$\text{Pd}(\text{OAc})_2$ , TBAC, $\text{Na}_2\text{CO}_3$ , $\text{HCOOH}$ , DMF, $80\text{ }^\circ\text{C}$	complex mixture
3	$\text{Pd}(\text{OAc})_2$ , $\text{PPh}_3$ , $\text{Et}_3\text{N}$ , $\text{HCOOH}$ , DMF, $80\text{ }^\circ\text{C}$	complex mixture
4	$\text{Pd}(\text{OAc})_2$ , $\text{PPh}_3$ , $\text{HCOONa}$ , DMF, $110\text{ }^\circ\text{C}$	complex mixture

We next tried terminating the Heck cascade via carbonylation, using the previously employed ligandless Heck conditions plus methanol and CO (1 atm.) (Scheme 3.23).<sup>96</sup> Unfortunately, rather than obtaining the desired product the unreacted starting material was recovered.

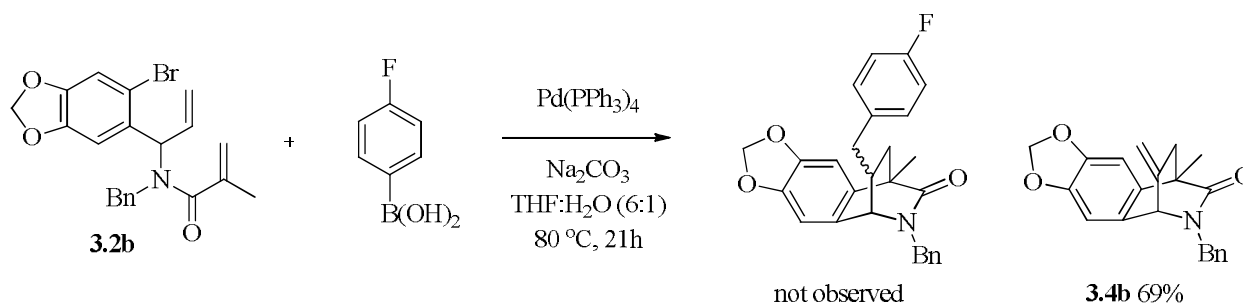
### Scheme 3.23



### Boronic Acid Termination

A third trapping method tested was termination via Suzuki coupling with a boronic acid (Scheme 3.24). This process, as described by Kim *et al.*, was seen as an attractive alternative due to the demonstrated ability to suppress  $\beta$ -hydride elimination and promote Suzuki termination. THF was injected into a reaction vessel containing the solid reagents including amide **3.2b** and tetrakis(triphenylphosphine)palladium, followed by (4-fluorophenyl)boronic acid in THF and  $\text{Na}_2\text{CO}_3$  (aq.). The resulting reaction mixture was stirred at 80 °C for 23 hours followed by purification via column chromatography to afford a white solid product. Much to our dismay we did not observe formation of the desired boronic acid terminated product; however, after purification we did obtain an interesting result. Analysis of the major product indicated that we had formed exclusively the *exo* isomer of bridged product **3.4b** in a 69% yield (Scheme 3.24). Based on this result, we determined that, although trapping prior to  $\beta$ -hydride elimination did not seem possible, synthesis of a single isomer was, and that the choice of solvent plays a key role.

### Scheme 3.24

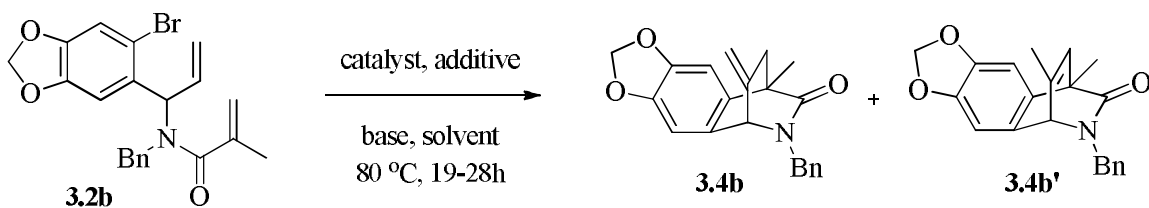


### 3.4.2 Heck Conditions for Single Isomer Formation

Over the course of this project we have explored various reaction conditions in an effort to achieve the single isomer formation (Table 3.7). We theorized that introduction of a more reactive base would speed up reductive elimination of H-Pd<sup>II</sup>-X, thereby diminishing the possibility for readdition of the catalyst. With this in mind we tried alternative bases including KOAc (Entry 2, Table 3.7) and Et<sub>3</sub>N (Entry 3, Table 3.7). However, in both cases we observed only a minimal change in the isomer ratio. In our next attempt we explored classic Heck conditions, using a PPh<sub>3</sub> ligand and Cs<sub>2</sub>CO<sub>3</sub> base (Entry 4, Table 3.7). Under these conditions we obtained a comparable mixture of isomers at a diminished yield of 54%. Another strategy involved the introduction of a silver salt, which has been shown to suppress catalyst readdition.<sup>74</sup> The Heck cascade reaction was run under the same conditions as in entry 3, with the addition of silver triflate to yield a highly impure product mixture (Entry 5, Table 3.7). Although analysis of the <sup>1</sup>H NMR seemed to indicate single isomer formation, purification greatly diminished its yield. Concurrently, we succeeded in single isomer formation via the previously mentioned boronic acid termination method. Continuing with this promising result the reaction was ran again under the same conditions without the boronic acid affording a 61% yield of the single isomer product (Entry 6, Table 3.7). In an effort to improve the yield the reaction was ran again, without the water and with an organic base (Et<sub>3</sub>N) and we were very pleased to observe a 90% yield of the desired product. (Entry 7, Table 3.7). We believe that choice of solvent plays a central role in single isomer formation. Via coordination, THF may not be stabilizing the H-Pd(II)-X intermediate as well as DMF would, causing reductive elimination to be faster and thereby avoiding readdition of the palladium species.

**Table 3.7**





Entry	Catalyst	Additive	Base	Solvent	Lactam 3.4b:3.4b' (%)	3.4b : 3.4b' <sup>a</sup> (%)
1	Pd(OAc) <sub>2</sub>	TBAC	Na <sub>2</sub> CO <sub>3</sub>	DMF	90 <sup>b</sup>	60 : 40
2	Pd(OAc) <sub>2</sub>	TBAC	KOAc	DMF	93 <sup>b</sup>	63 : 37
3	Pd(OAc) <sub>2</sub>	TBAC	Et <sub>3</sub> N	DMF	90 <sup>b</sup>	66 : 34
4	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	DMF	54 <sup>b</sup>	67 : 33
5	Pd(OAc) <sub>2</sub>	TBAC/ AgOTf	Et <sub>3</sub> N	DMF	60 <sup>c</sup>	100 : 0
6	Pd(PPh <sub>3</sub> ) <sub>4</sub>	-	Na <sub>2</sub> CO <sub>3</sub>	THF/H <sub>2</sub> O	61 <sup>c</sup>	100 : 0
7	Pd(PPh <sub>3</sub> ) <sub>4</sub>	-	Et <sub>3</sub> N	THF	90 <sup>c</sup>	100 : 0

<sup>a</sup>Molar ratio of the regioisomers established by <sup>1</sup>H NMR. <sup>b</sup>Combined isolated yield of an inseparable mixture of two regioisomers. <sup>c</sup>Isolated yield of a single compound.

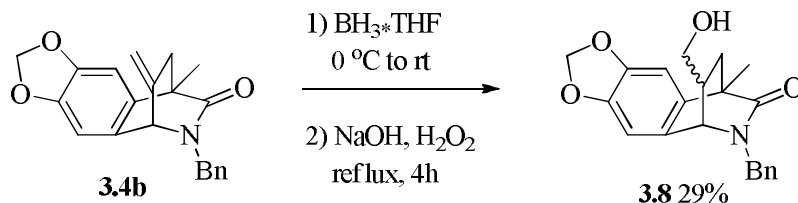
### 3.5 Reactions with the Bridgehead Olefin in the Single Regioisomer

Once we had successfully achieved single isomer formation we next endeavored to explore diversification of the bridgehead olefin. A major advantage in this scenario was that because we were not trying to convert a mixture of products to a single product (through a common intermediate), we could utilize protocols for functionalization of terminal olefins. With this in mind, we proposed diversification via either hydroboration or cross-metathesis.

#### 3.5.1 Hydroboration

Initial attempts at hydroboration of lactam **3.4b** afforded a 29% yield of what appeared to be alcohol **3.8** (Scheme 3.25). However I was unable to clearly discern the outcome, leading me to abandon hydroboration for the more desirable cross-metathesis method.

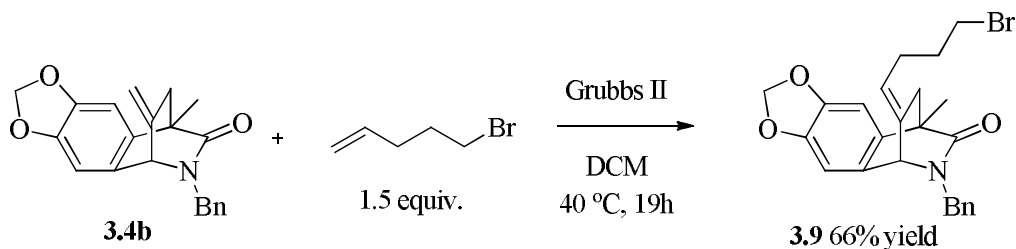
#### Scheme 3.25



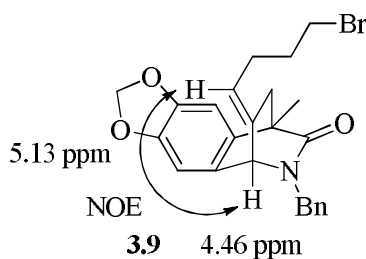
### 3.5.2 Cross Metathesis

Cross metathesis was seen as an attractive possibility because it would coincide nicely with our goal of developing a transition metal-catalyzed sequence. As demonstrated in the literature,<sup>127a, 127b, 128</sup> cross metathesis is a powerful method for incorporating a flexible tether onto the substrate scaffold. Considering this, we endeavored to explore cross metathesis of our single isomer product (**3.4b**) and a subsequent nucleophilic substitution in order to attach a second potentially biologically active fragment to our isoquinuclidine core, via a flexible tether. A solution of our single isomer lactam (**3.4b**) in DCM was added to a pressure tube containing Grubbs II catalyst, followed by the addition of neat 5-bromopent-1-ene. The pressure tube was then flushed with argon, sealed and the mixture stirred at 40 °C over night (18 h). Purification via column chromatography afforded a 66% yield of cross metathesis product **3.9** (Scheme 3.26).

**Scheme 3.26**



Selective irradiation NOE analysis of **3.9** was used to establish the relative stereochemistry of the olefin in an *E* configuration (Figure 3.5). Irradiation of the vinylic proton at 5.13 ppm showed an enhancement of the methine proton at 4.46 ppm.

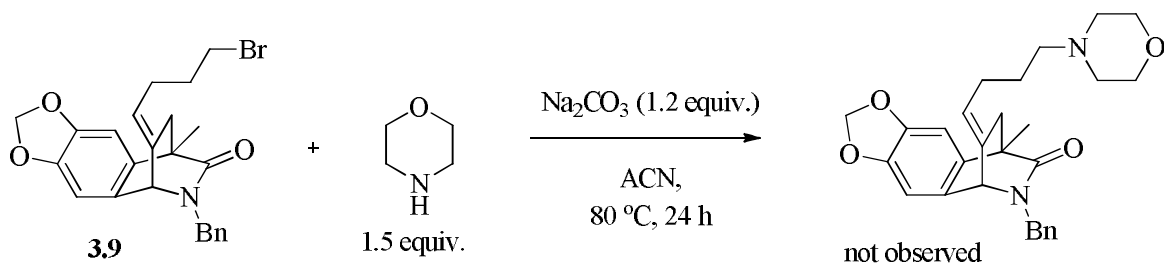


**Figure 3.5**  $^1\text{H}$  NMR NOE of alkyl bromide **3.9**

### 3.6 Nucleophilic Substitution

Once we had successfully accessed cross metathesis product **3.9**, our next goal was to explore substitution with a biologically relevant nucleophile. For our first attempt we selected morpholine as the nucleophile because the desired product would nicely mimic existing drug scaffolds.<sup>171a</sup> However, although the starting material was consumed, no substitution product was observed (Scheme 3.27). Unfortunately, we were unable to determine what happened to the starting material, but we do believe that use of a stronger base (possible NaH)<sup>172</sup> would facilitate nucleophilic substitution.

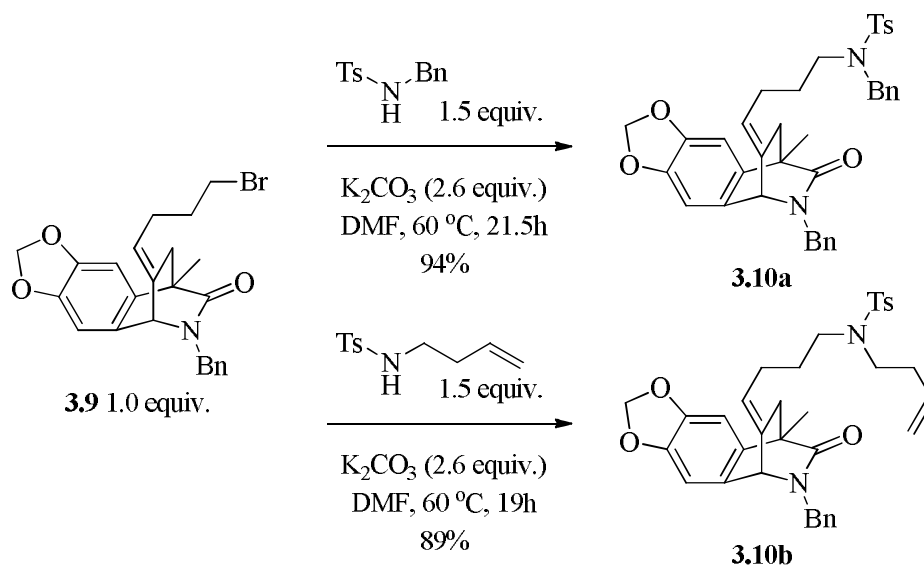
#### Scheme 3.27



In addition to morpholine, we also investigated the use of sulfonamide nucleophiles. Sulfonamide addition would not only attach a group with biological potential to the existing scaffold,<sup>171b</sup> but would also make additional diversification via *N*-functionalization possible. The desired sulfonamides were obtained in a single step from tosyl chloride and the corresponding amine according to a literature precedent.<sup>98, 173</sup> A solution of alkyl bromide **3.9** (1.0 equiv.) in

dry DMF (2 mL) was added dropwise, at room temperature, to a mixture of *N*-benzyl-4-methylbenzenesulfonamide (1.5 equiv.) and anhydrous K<sub>2</sub>CO<sub>3</sub> (2.6 equiv.) in dry DMF (1 mL). The reaction mixture was stirred at 60 °C for 21.5 h and the crude product purified by prep-TLC to afford bis amide **3.10a** in a 94% yield. Substitution with an alternative *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide nucleophile afforded bis amide **3.10b** in a 89% yield (Scheme 3.28). As observed, using cross methathesis and a subsequent nucleophilic substitution, we have been able to obtain a product with two potentially reactive functionalities linked together via a flexible alkyl tether. This novel molecular scaffold seems well suited for further diversification or biological screening.

#### Scheme 3.28



#### Conclusion

In conclusion, I have developed a palladium-catalyzed method for obtaining a novel aryl-fused azabicyclooctane ring system. Initially, Heck cyclization afforded the desired product as a mixture of regioisomers, which we attempted to resolve via allylic substitution; however, this method proved impractical. Returning to the Heck conditions, I was able to obtain the desired

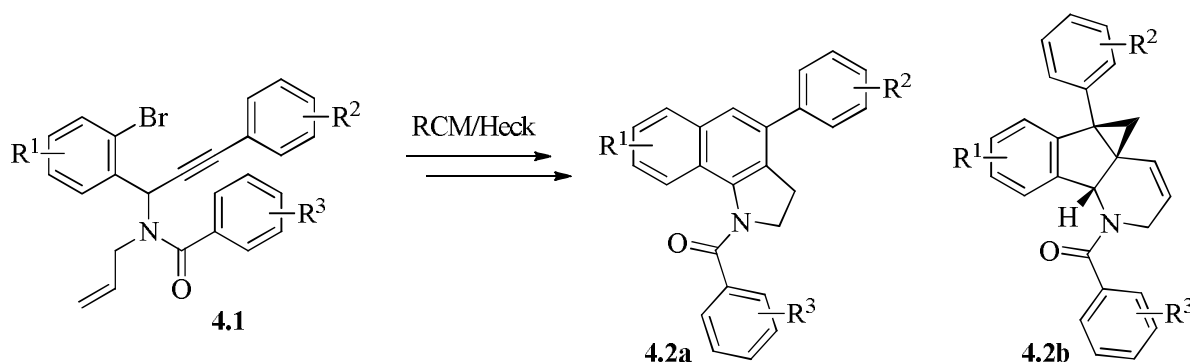
product as a single *exo* regioisomer. Cross metathesis, followed by nucleophilic substitution, allowed us to attach a sulfonamide functionality to the bridged core via a flexible tether, affording a novel alkaloid-type structure which we intend to submit for biological screening. In addition, we hope to see this method applied to combinatorial library synthesis, in order to perform a more extensive diversification of the three-component coupling agents, cross metathesis partner and the substitution agent.

## **Chapter Four**

### *Synthesis of Functionalized Aryl-Fused Azabicyclo[2.2.2]octanes via Radical Cyclization*

Another area of interest in the Malinakova group is use of the copper-catalyzed three-component coupling method to construct amide tethered enynes which can then be cyclized through various annulation pathways. Previous efforts in our lab have utilized sequential RCM/Heck annulations on amide tethered enyne **4.1** to achieve divergent synthesis of fused *N*-heterocyclic scaffolds **4.2a** and **4.2b** (Scheme 4.1).<sup>179</sup> As a continuation of our long-term goal to achieve divergent synthesis of polycyclic *N*-heterocyclic scaffolds, we were also seeking alternative reaction pathways.

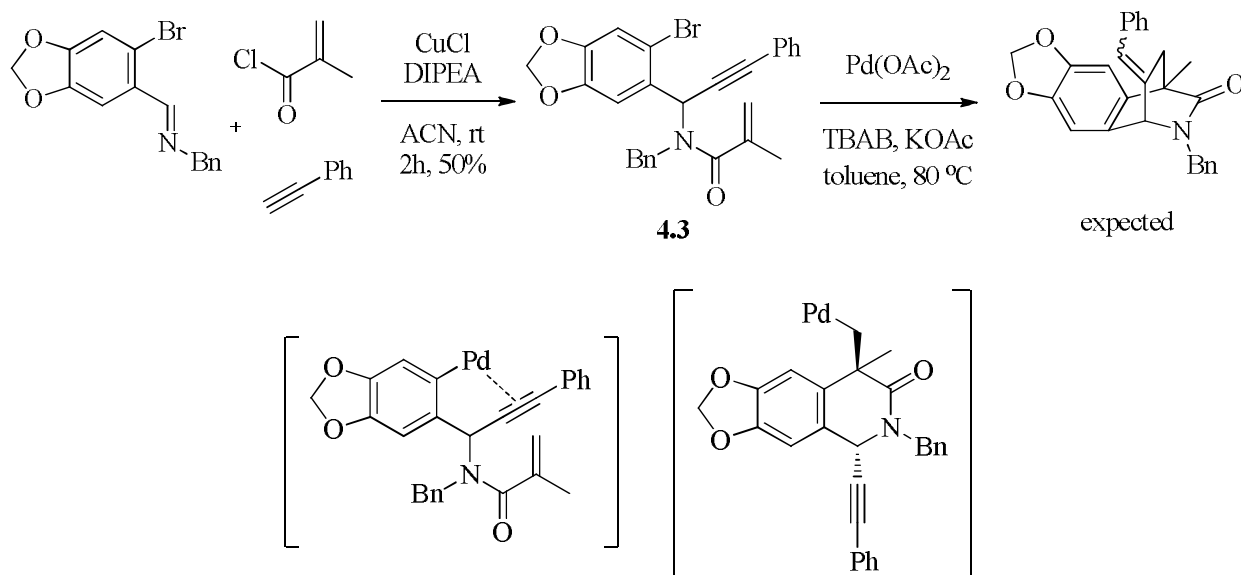
**Scheme 4.1**



Just as with my first project, one promising annulation method that we hoped to apply was the Heck cascade method. However, to achieve bridge formation via a Heck cascade process it was necessary to slightly redesign amide scaffold **4.1**. To avoid  $\beta$ -hydride elimination after the first cyclization, we deemed it necessary to add a methyl substituent to the olefin. With this in mind, I synthesized amide tethered enyne **4.3** under standard copper-catalyzed three-component coupling conditions<sup>114</sup> in a 50% yield (Scheme 4.2). Amide **4.3** was then treated with Jeffery's ligandless Heck conditions<sup>67</sup> unfortunately affording a complex indiscernible reaction mixture. Our current hypothesis is that reaction failure is due to two possible complications. Chelation of the aryl palladium to the alkyne could have quenched the cyclization; alternatively, following the first cyclization the alkyl palladium and alkyne may have been on opposite faces of

the amide, thereby disallowing the second cyclization (Figure 4.1). More experimentation is needed to determine exactly what went wrong and how it might be corrected.

#### Scheme 4.2



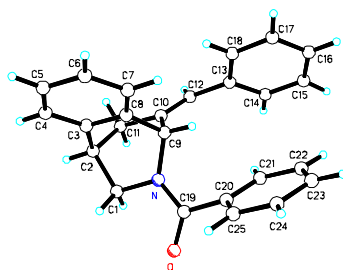
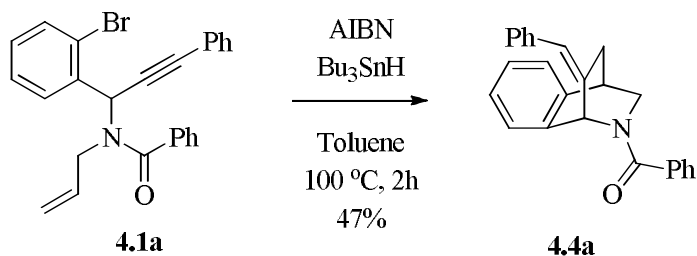
**Figure 4.1** Possible complications in Heck cyclization of amide **4.3**

#### 4.1 Method Development, Mechanism

While finalizing his results on the previously mentioned RCM/Heck sequence<sup>179</sup> my colleague, Sandeep Raikar, serendipitously attempted radical cyclization of amide tethered enyne **4.1a** and was pleased to observe the formation of a bridged product (**4.4a**) in a 47% yield (Scheme 4.3). He was also able to assign the relative *Z* stereochemistry of the olefin after obtaining an X-ray crystal structure of **4.4a** (Figure 4.2). Contrary to the Heck cascade reaction, amide **4.1a** is well suited for a radical cyclization reaction because, under these conditions,  $\beta$ -hydride elimination is no longer a problem. Observing the striking similarity of product **4.4a** to the bridged scaffold constructed in my first project, I moved forward with optimization of this radical cascade method.

#### Scheme 4.3



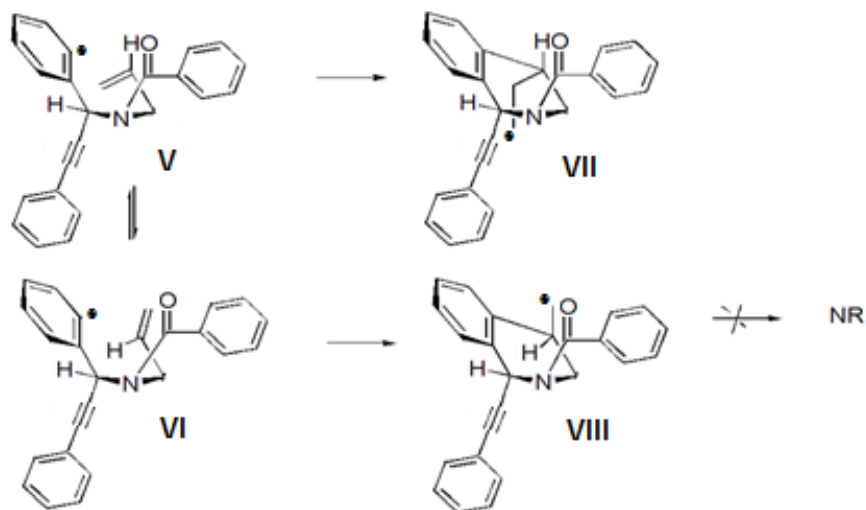


**Figure 4.2** *X-ray crystal structure of 4.4a*

In order to optimize the radical cascade reaction, we first needed to consider the mechanism, including the stereoselectivity of cyclization. For this we envisioned a conformation of the substrate very similar to that proposed for the Heck cascade reaction above. Following radical initiation, an equilibrium would exist between two conformations of the pre-cyclization intermediate (**V** and **VI**), both having the alkyne and *N*-benzoyl protecting group in a low energy *anti* configuration (Scheme 4.4). The aryl radical can then approach the olefin from one of two possible diastereotopic faces. Although the steric interactions and therefore the presumed energy difference between **V** and **VI** is not as significant as was the case for the Heck cyclization, approach from the *re* face would lead to intermediate **VIII** with the alkyl radical and *N*-benzoyl on the same face. This would also place the alkyl radical on the opposite face from the alkyne, thereby disallowing the second cyclization event. Alternatively, approach from the *si* face would lead to intermediate **VII** with the alkyl radical and alkyne on the same face of the ring, allowing for a rapid second cyclization step to proceed. Thus, just like with the Heck cascade, an

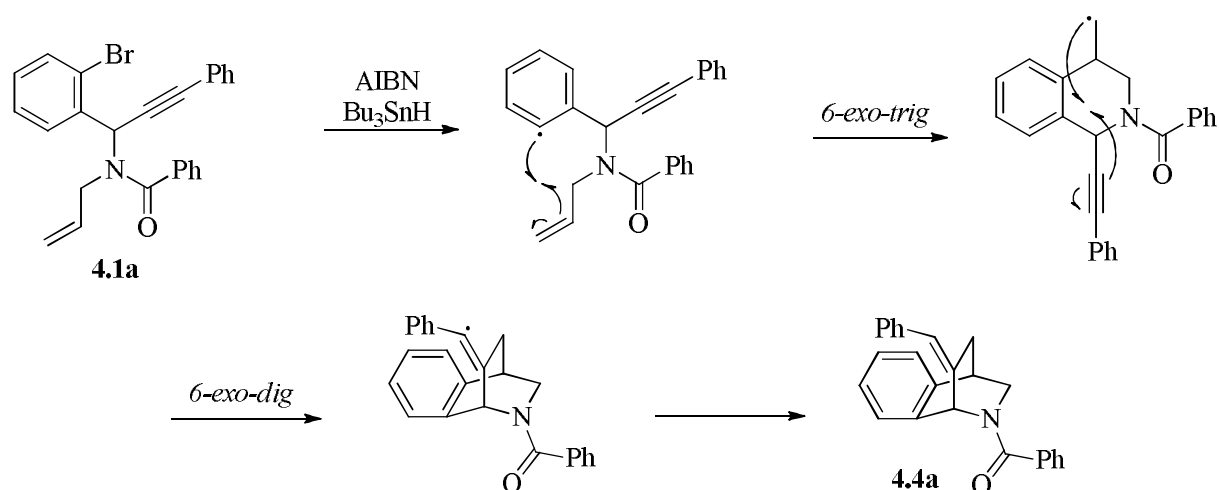
equilibrium between conformations **V** and **VI** would cause all the substrate to be converted to desired intermediate **VIII**.

**Scheme 4.4**



Our proposed mechanism begins with radical initiation on **4.1a** to generate an aryl radical intermediate (Scheme 4.5). Sequential *6-exo-trig*, *6-exo-dig* cyclization would generate a vinyl radical intermediate, followed by termination to afford bridged product **4.4a**. It is important to note that vinyl radicals are not configurationally stable,<sup>180</sup> therefore just as the catalyst readdition was an issue in the Heck reaction, interconversion between the *Z* and *E* stereoisomers of the vinyl radical proved to be a cause for the formation of stereoisomers.

**Scheme 4.5**



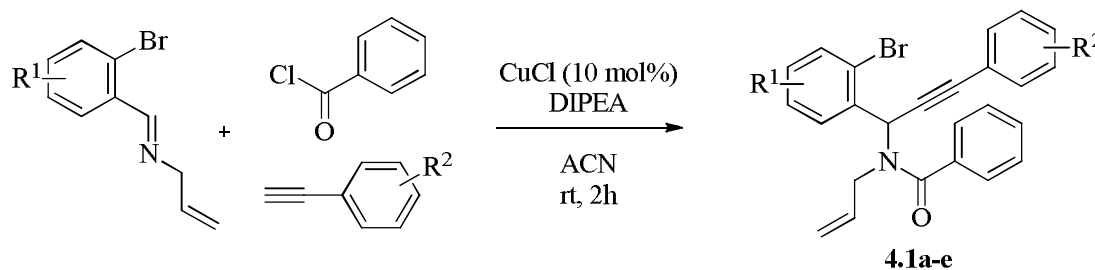
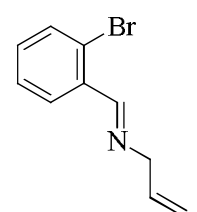
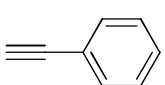
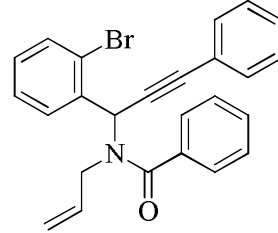
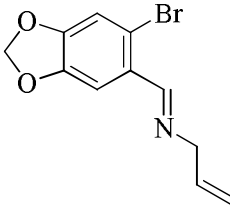
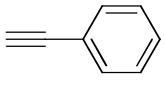
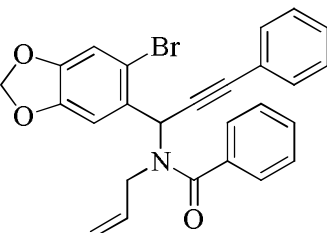
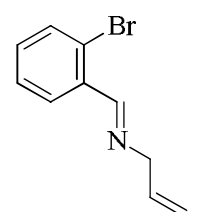
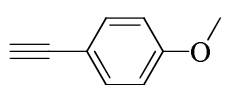
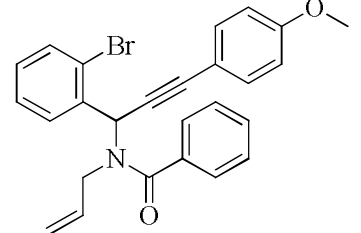
## 4.2 Cu-Catalyzed Three-Component Coupling

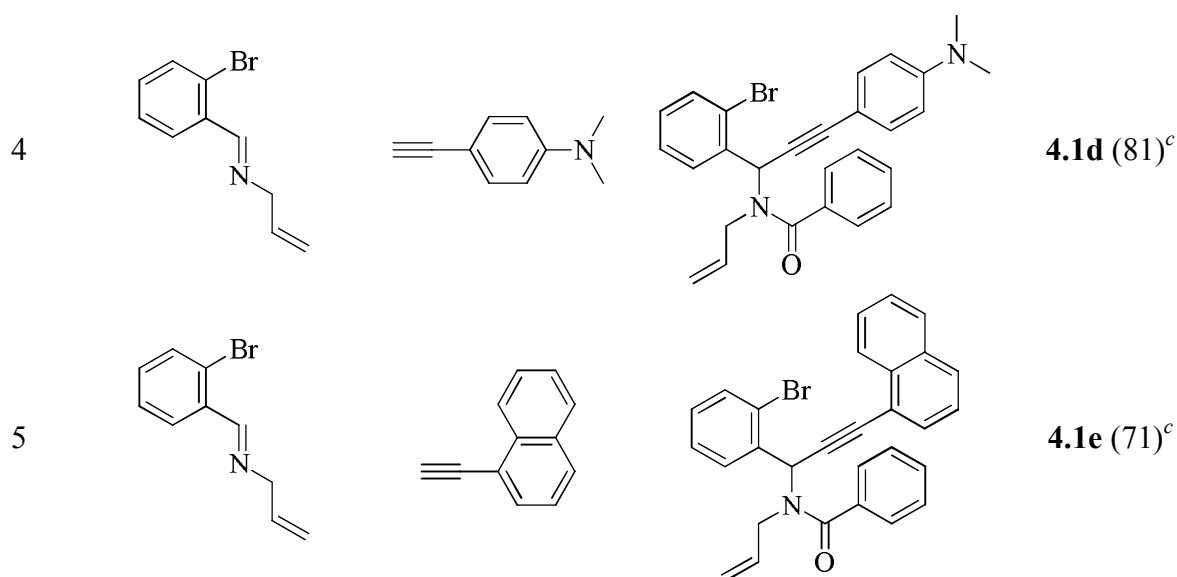
We next set out to synthesize a series of amide tethered enyne analogues, by varying the three reactants. The desired amides (**4.1a-e**) were easily synthesized in a single step via copper-catalyzed three-component coupling between an imine, benzoyl chloride and alkyne (Table 4.1).

<sup>114</sup> A solution of imine<sup>181</sup> (1.0 equiv.), benzoyl chloride (1.2 equiv.) and alkyne (1.5 equiv.) in ACN (0.34 M) was stirred at room temperature for an average of 30 minutes, allowing time for acyl iminium formation. Concurrently, a separate solution was prepared containing CuCl (20 mol%) in ACN (0.67 M). The resulting solution and neat DIPEA (1.5 equiv.) were added dropwise simultaneously to the CuCl solution. This mixture was then allowed to stir at room temperature for two hours, followed by purification via column chromatography to afford enynes **4.1a-e**. Using these standard conditions I synthesized a series of amide tethered enynes with various substituents on the aryl imines and aryl alkynes (Table 4.1). Known compounds **4.1a** and **4.1c** (previously employed in our lab in an RCM/Heck sequence)<sup>179</sup> were prepared in good yields to investigate their utility in the radical cascade process (Entry 1 and 3, Table 4.1). Original compound **4.1b** was also prepared, in a 69% yield, to explore the effects of variation in the aryl bromide fragment (Entry 2, Table 4.1). In this project we sought to explore

functionalization of the bridgehead olefin by changing the initial alkyne substrate rather than diversification of a common core in the final step. Considering this, I also prepared two new compounds, **4.1d** and **4.1e**, with alternative alkynes 4-ethynyl-*N,N*-dimethylaniline and 1-ethynynaphthalene respectively (Entry 4-5, Table 4.1).

**Table 4.1**

				
Entry	Imine	Alkyne	Amide 4.1	Amide 4.1 (%) <sup>a</sup>
1				<b>4.1a</b> (81) <sup>b</sup>
2				<b>4.1b</b> (69) <sup>c</sup>
3				<b>4.1c</b> (74) <sup>b</sup>



<sup>a</sup>Isolated yield of a single compound. <sup>b</sup>Known compound synthesized according to literature precedent.<sup>179</sup> <sup>c</sup>Original compound synthesized according to literature precedent.

## 4.3 Radical Cascade

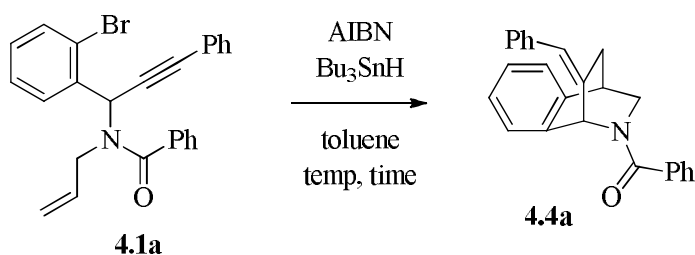
As previously stated, my colleague had achieved a 47% yield of aryl-fused isoquinuclidine **4.4a**, as a single stereoisomer (Entry 1, Table 4.2). In an effort to improve the yield I moved forward to explore variations in time, temperature, reactant loading and concentration.

### 4.3.1 Optimization of Conditions

For my first trial I increased the reaction mixture concentration and obtained a much lower, 11% yield of azabicyclooctane **4.4a** (Entry 2, Table 4.2). This led us to believe that lower concentration facilitated the reaction; however we later discovered that purity of the amide starting material (**4.1a**) was the primary cause of the low yield. After successive trials (not shown) and careful analysis of the starting material <sup>1</sup>H NMR, we determined that even a slight amount of DIPEA left over from the three-component coupling reaction would hinder the radical process. After resolving this issue we ran the reaction again with an increased loading of tributylstannane and AIBN and obtained a modest 55% yield of **4.4a** (Entry 3, Table 4.2).

Lowering the reaction temperature to 80 °C afforded a slightly lower yield of 52% (Entry 4, Table 4.2). After realizing that concentration was not the likely cause of the low yield in entry 2, I ran the reaction again, varying the equivalents and temperature, at a lower concentration affording a 50% yield of the product (Entry 5, Table 4.2). Finally, decreased loading of the tributylstannane and AIBN was tested yielding bicyclooctane **4.4a** in a comparable 50% yield (Entry 6, Table 4.2). Clearly, this remains a work in progress with additional optimization needed. The next reasonable course of action would be to lower the equivalents of the two reactants at a higher temperature.

**Table 4.2**



Entry	Bu <sub>3</sub> SnH (equiv.)	AIBN (equiv.)	Toluene (mM)	Temp (°C)	Time (h)	Yield <b>4.4a</b> <sup>a</sup> (%)
1	1.5	0.1	18	100	1	47
2 <sup>b</sup>	1.5	0.1	27	100	2	11
3	2.0	0.5	16	100	3	55
4	2.0	0.5	16	80	5.5	52
5	2.0	0.5	37	80	5	50
6	1.1	0.1	13	80	1.5	50

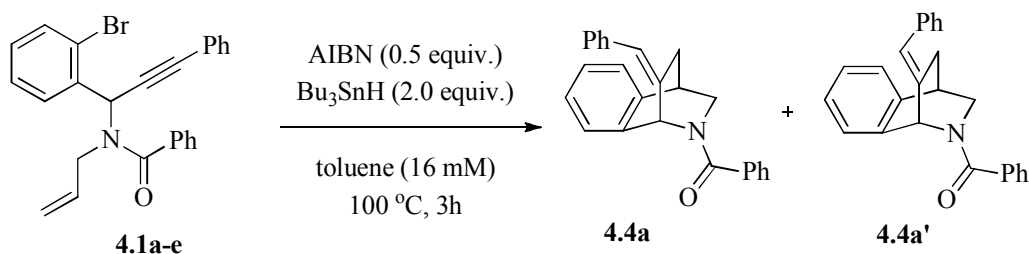
<sup>a</sup>Isolated yield of a single compound. <sup>b</sup>Impure amide **4.1a** starting material sample.

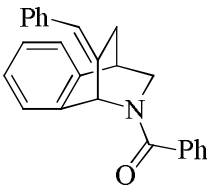
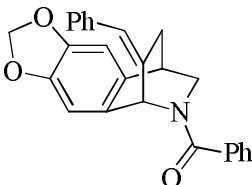
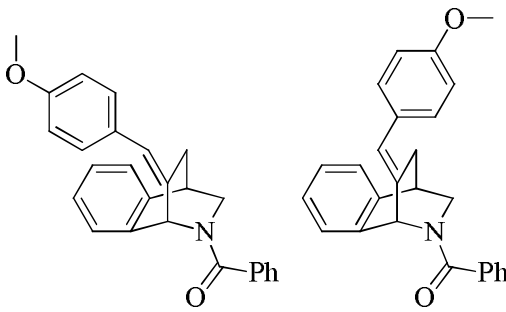
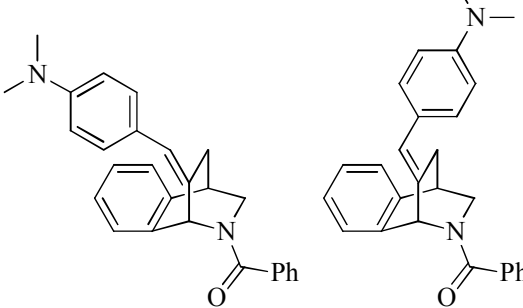
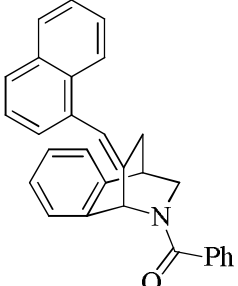
### 4.3.2 Synthesis of Analogues

While continuing to investigate optimization of the radical cascade process I moved forward with the synthesis of bicyclooctane **4.4** analogues. We hypothesized that maybe an electron rich substrate would prove more conducive to the radical process, through stabilization of the radical intermediate. All entries employed the conditions outlined in Table 4.3, Entry 3,

and the following standard procedure. A solution of amide **4.1** in toluene was injected into a reaction flask charged with AIBN, followed by addition of neat tributylstannane. The resulting solution was stirred at 100 °C for three hours then purified by column chromatography to afford bicyclooctane **4.4**. Radical cyclization of electron rich amide **4.1b** afforded bicyclooctane **4.4b** in an improved yield of 62%, when compared to unsubstituted analogue **4.4a** (Entry 1-2, Table 4.3). As predicted, an electron rich substituent on the aryl bromide fragment stabilized the radical intermediate and thereby affording an improved yield. This conclusion was further supported when radical cyclization of amide **4.1c** afforded a 63% yield of the bicyclooctane product (Entry 3, Table 4.3). However, in this instance the product was isolated as an inseparable mixture of *Z* and *E* isomers, **4.4c** and **4.4c'** respectively. The proposed rationale for the observed isomer formation is that the electron rich substituent on the aryl alkyne fragment stabilizes the vinylic radical, increasing its lifetime and thereby allowing an interconversion of the *Z* and *E* stereoisomers. Running the reaction at a lower temperature may reduce the occurrence of isomerization, however this hypothesis remains to be investigated. Radical cyclization of electron rich amide **4.1d** also afforded the bicyclooctane product as an inseparable mixture of stereoisomers **4.4d** and **4.4d'**, in a diminished yield of 43% (Entry 4, Table 4.3). Finally, cyclization of naphthalene analogue **4.1e** produced bicyclooctane **4.4e** as a single stereoisomer, in a 56% yield (Entry 5, Table 4.3).

**Table 4.3**



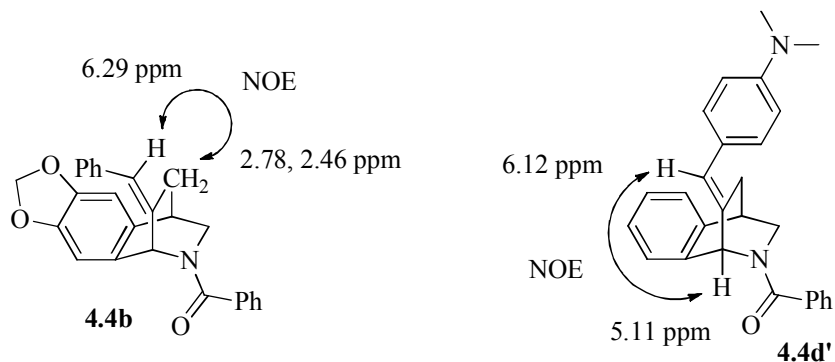
Entry	Amide 4.1	Bicyclooctanes 4.4	Bicyclooctanes 4.4 (%)
1	4.1a		4.4a (55) <sup>a</sup>
2	4.1b		4.4b (62) <sup>a</sup>
3	4.1c		4.4c and 4.4c' (63) <sup>b</sup>
4	4.1d		4.4d and 4.4d' (43) <sup>b</sup>
5	4.1e		4.4e (56) <sup>a</sup>

<sup>a</sup>Isolated yield of a single compound. <sup>b</sup>Combined isolated yield of an inseparable mixture of two regioisomers (70% and 30% respectively).

Using <sup>1</sup>H NMR NOE analysis, I confirmed the *Z* olefin stereochemistry of **4.4b**, already assigned to by the X-ray crystallography of **4.4a** (Figure 4.2). Irradiation of the vinylic proton at



6.29 ppm caused an enhancement in the methylene protons at 2.78 and 2.46 ppm. The relative stereochemistry of minor isomer **4.4d'** was also assigned as an *E* configuration using  $^1\text{H}$  NMR NOE analysis, performed on the mixture of isomers **4.4d** and **4.4d'**. Irradiation of the methine proton at 5.11 ppm, assigned to the minor isomer, caused an enhancement of the vinylic proton at 6.12 ppm, assigned to the minor isomer.



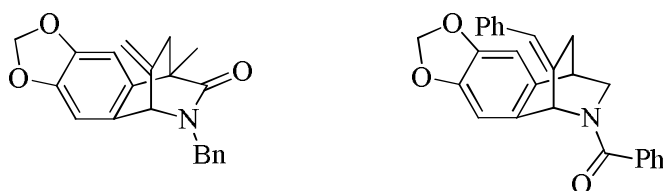
**Figure 4.3**  $^1\text{H}$  NMR NOE of azabicyclooctanes **4.4b** and **4.4d'**

## Conclusion

In conclusion, we have developed a radical cyclization method for obtaining an alternative bridged azabicyclooctane scaffold. Future efforts will explore optimization of the conditions to improve yield as well as synthesis of additional analogues with biologically relevant substituents.

A comparison of the two methods (Heck vs. radical cascade) provides insight into their distinct advantages and disadvantages (Figure 4.4). To begin with, both methods achieve rapid formation of the bridged core in a single step via formation of two new C-C bonds. Another key component is their ability to obtain the azabicyclooctane scaffold with transposition of the carbonyl component, a feat often difficult to achieve using functional group interconversion. Using the Heck cascade method I was able to obtain the bridged lactam scaffold in generally high yields, however the method was plagued by isomerization issues. In addition,

diversification of the exocyclic olefin has thus far required an additional synthetic step (cross metathesis). This issue may be resolved in the future during library synthesis by variation in the vinyl tin component. In comparison, the radical cascade method affords the azabicyclooctane scaffold in a relatively low yield. Here also, isomerization has been an issue, however only in select electron rich cases. The radical method also allows for diversification of the olefin substituent via variation in the aryl alkyne starting material, thereby avoiding the need for additional synthetic steps. Overall, we have provided two promising and complementary strategies for construction of the azabicyclooctane core, which would be well suited for combinatorial library synthesis.



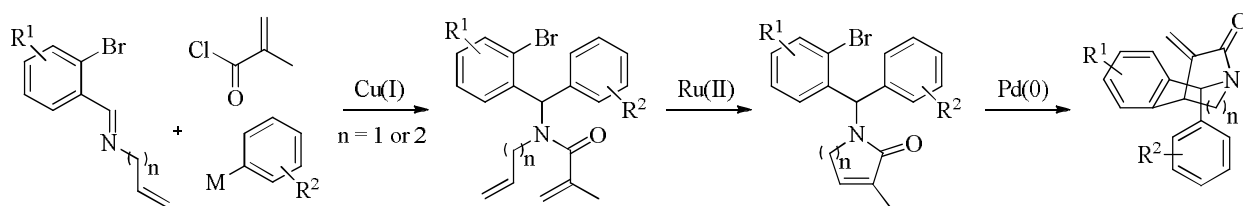
**Figure 4.4** Azabicyclooctane products obtained via Heck and radical cascade method.

## **Chapter Five**

*Attempts at Developing a Sequential Ru/Pd Protocol for the Synthesis of Bridged N-Heterocycles*

For my third project we chose to shift gears and explore the formation of an alternative bridged *N*-heterocyclic scaffold. Previously published work in the Malinakova group has accomplished efficient synthesis of fused *N*-heterocycles via a sequential RCM/Heck process.<sup>179</sup> Hoping to expand the potential application of this sequential method, my proposal was to run two sequential transition metal-catalyzed reactions (RCM/Heck) on a three-component coupling-derived amide to obtain a novel bicyclobenzazepine ring system (Scheme 5.1). Once the protocol had been sufficiently developed, we then intended to adapt the method to one-pot synthesis.<sup>182</sup> Although similar methods have been employed by Grigg<sup>130-131</sup> and Martin,<sup>44-45, 110b</sup> major advantages to this proposal include the presence of two easily diversifiable aryl substituents ( $R^1$  and  $R^2$ ) and the availability of a reactive Michael acceptor for further scaffold diversification (Scheme 5.1). We were also aware that our proposed bicyclobenzazepine structure contained a twisted bridgehead amide. Although this structural motif is highly strained and often challenging to construct, similar complexes have been made before. What follows is a description of our preliminary efforts at developing this three-step transition metal-catalyzed process and the challenges faced therein.

**Scheme 5.1**

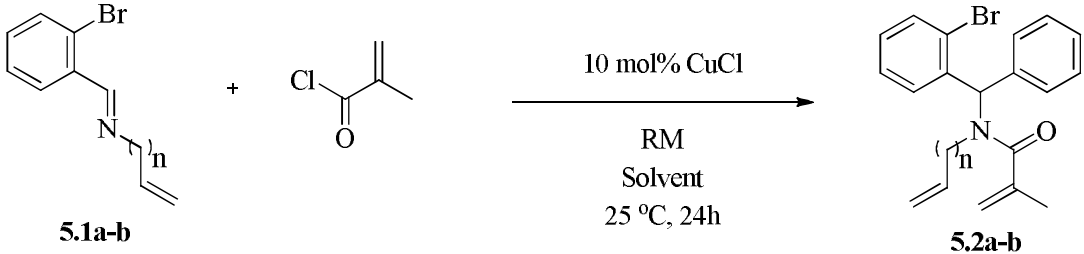
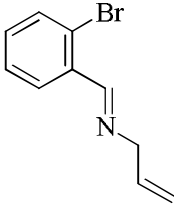
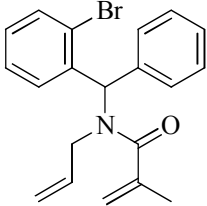
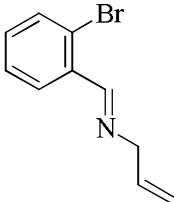
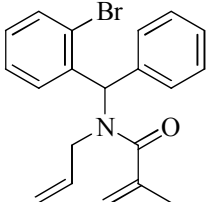


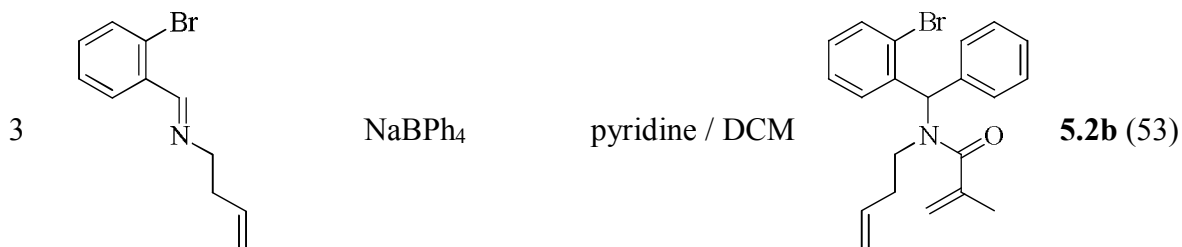
### 5.1 Cu-Catalyzed Three-Component Coupling

For this project I once again needed to adapt the Arndtsen three-component process to my specific needs. In this case, we were interested in nucleophilic addition of aryl-metal components (RM) to the acyl iminium intermediate (Table 5.1). Initially, we attempted the

three-component coupling using an aryltin reagent; however, in spite of the literature precedent,<sup>113</sup> we were unable to obtain the desired amide; presumably due to a slow transmetallation of the aryl tin reagent (Entry 1, Table 5.1). Expanding on a recent publication by Arndtsen,<sup>116</sup> we next attempted three-component coupling with an organoborane reagent and were pleased to observe formation of amides **5.1a-b** (Table 5.1). Copper-catalyzed three component coupling between imine **5.1a** ( $n = 1$ ), methacryloyl chloride and sodium tetraphenylborate afforded amide **5.2a** in a modest 55% yield (Entry 2, Table 5.1). Homoallyl adduct **5.2b** was also obtained in a 53% yield, via three-component coupling with imine **5.1b** (Entry 3, Table 5.1). Currently, the use of aryl-metal components in the three-component coupling process is underdeveloped. In the future we would like to see this method adapted and expanded to allow addition of aryl as well as heteroaryl boron reagents.

**Table 5.1**

					
Entry	Imine 5.1	RM	Solvent	Amide 5.2	Amide 5.2 (%) <sup>a</sup>
1		SnPhBu <sub>3</sub>	ACN / DCM		-
2		NaBPh <sub>4</sub>	pyridine / DCM		<b>5.2a</b> (55)

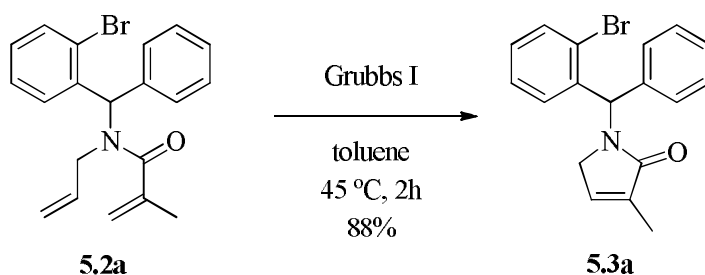


<sup>a</sup>Isolated yield of a single compound.

## 5.2 Sequential RCM/Heck Annulations

My next goal was to explore sequential Ru/Pd catalysis on amides **5.2a-b**. Contrary to the literature precedent, ring-closing metathesis of amide **5.2a**, using Grubbs I catalyst, easily afforded  $\gamma$ -lactam **5.3a** in an 88% yield (Scheme 5.2).

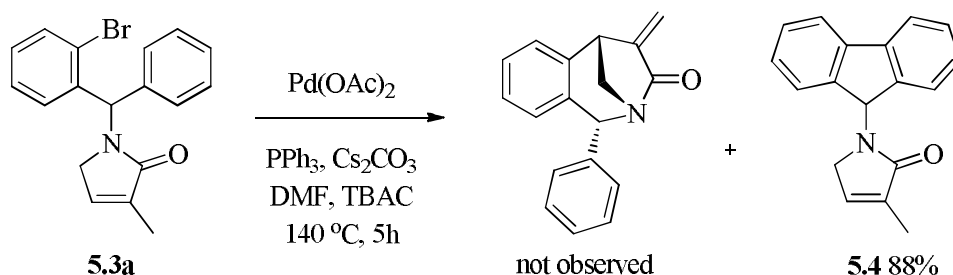
### Scheme 5.2



Unfortunately, palladium-catalyzed Heck cyclization of  $\gamma$ -lactam **5.3a** failed to produce the desired bicyclobenzazepine scaffold, forming instead aryl-fused product **5.4** (Scheme 5.3). Assuming that aryl-fused product formation was due to the high temperature (140 °C), the reaction was run again at lower temperatures (100 °C and 80 °C); however, in both cases neither of the products were obtained. Although this confirmed our concern about the high temperature, we were disappointed that we had not obtained the desired bridged product. Our current working hypothesis is that conformational strain, imparted to the starting material (**5.3a**) by the presence of the lactam functionality, does not allow the aryl palladium and olefin to get in a close enough proximity for the cyclization to proceed. We also proposed that the most likely solution to this

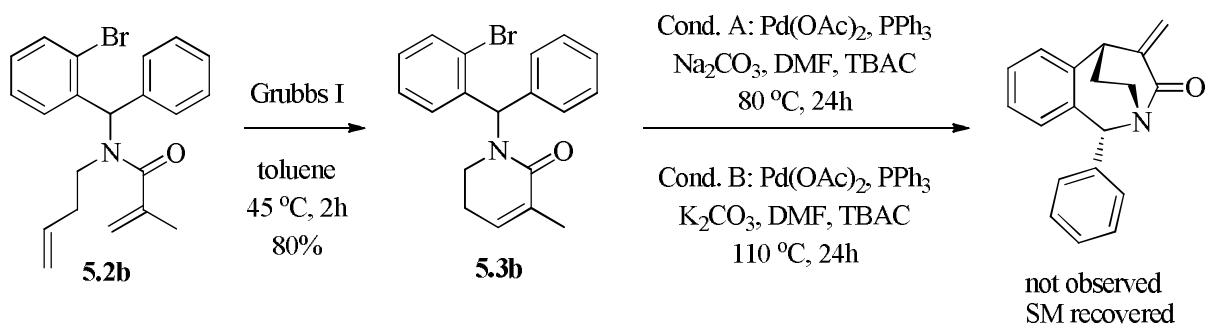
problem would be increasing the lactam ring size, thereby imparting greater flexibility to the molecule.

### Scheme 5.3



To investigate our ring size hypothesis, Grubbs I-catalyzed ring-closing metathesis was performed on *N*-homoallyl amide **5.2b** affording  $\delta$ -lactam **5.3b** in a 80% yield (Scheme 5.4). Heck cyclization was then attempted on  $\delta$ -lactam **5.3b** with  $\text{Na}_2\text{CO}_3$  at  $80\text{ }^\circ\text{C}$  and  $\text{K}_2\text{CO}_3$  at  $110\text{ }^\circ\text{C}$ . Unfortunately, in spite of the larger lactam ring size, we once again failed to observe bicyclobenzazepine formation, and only recovered the starting material.

### Scheme 5.4



### Conclusion

In conclusion, we have proposed a sequential transition metal-catalyzed RCM/Heck method of obtaining the bicyclobenzazepine scaffold. However, although three-component coupling and ring-closing metatheses were both easily accomplished, we have thus far been unable to achieve Heck cyclization of the lactam intermediate. Clearly, conformational issues

are a major problem for this method and greater exploration of Heck conditions should be undertaken. One possibility I would like to see attempted is use of microwave Heck conditions.<sup>133</sup> Another interesting avenue we have not yet explored would be radical cyclization conditions. In spite of our inability to obtain the desired bridged product, we have successfully synthesized interesting  $\gamma$ - and  $\delta$ -lactam products (**5.3**). Formation of these lactams, followed by coupling of the aryl halide with an organometallic agent and addition of a biologically relevant nucleophile into the available Michael acceptor would constitute an excellent project for combinatorial library synthesis.



## **Chapter Six:**

### *Experimental*

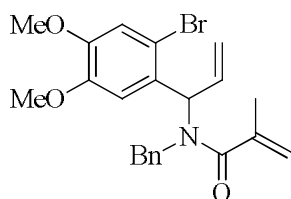
## General Experimental

Unless otherwise indicated, all NMR data were collected at room temperature in CDCl<sub>3</sub> with internal CHCl<sub>3</sub> as the reference (7.26 ppm for <sup>1</sup>H and 77.16 ppm for <sup>13</sup>C). IR spectra were measured in thin films on salt (NaCl) plates. MS were measured under fast atom bombardment (FAB) or electron impact (EI) conditions. Analytical thin-layer chromatography (TLC) was carried out on commercial Merck silica gel 60 plates, 0.25 mm thickness, with fluorescent indicator (F-254) or stained with aqueous KMnO<sub>4</sub> solution. Column chromatography was performed with 40-63 mm silica gel (Sorbent). Dichloromethane (DCM), Acetonitrile (ACN) and dimethylformamide (DMF) was distilled from CaH and kept over 3 Å (8-12 mesh) molecular sieves under an atmosphere of dry argon. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Triethyl amine was distilled from KOH and kept over 3 Å (8-12 mesh) molecular sieves under an atmosphere of dry argon; other solvents were used as received.<sup>183</sup>

Unless otherwise specified, all reactions were carried out under an atmosphere of dry argon in oven-dried (at least 6 h at 140 °C) glassware. All imines were prepared according to a modified literature procedure<sup>181</sup> by condensation of a 1:1 mixture of aldehyde and amine in methylene chloride (25 °C) in the presence of activated 3 Å (8-12 mesh) molecular sieves for 4-6 h (monitored by <sup>1</sup>H NMR) followed by filtration through celite and removal of solvent under vacuum to afford pure imines. All sulfonamides were prepared according to a modified literature procedure<sup>98</sup> by stirring a solution of amine (1.0 equiv.), tosyl chloride (1.2 equiv.) and Et<sub>3</sub>N (2.3 equiv.) in methylene chloride (25 °C) for 24 h, followed by column chromatography to afford pure sulfonamides. Other materials were used as received from commercial suppliers.

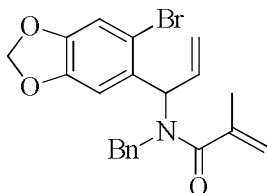
**General protocol for the preparation of amides 3.2a-n.** Neat acid chloride (1.3 equiv) was injected into a reaction vessel containing a solution of imine (1.0 equiv), CuCl (0.1 equiv) and

ACN (0.28 M). The reaction was stirred at room temperature for 30 minutes then a solution of tributylvinyltin (1.2 equiv) in DCM (0.14 M) was added dropwise. The reaction mixture was stirred at 45 °C for 6h, under argon, cooled, diluted with saturated aqueous KF (12 mL) and stirred for 16 h. Water was added (10 mL) and the mixture was extracted with EA (3x30 mL). The combined organic phase was washed with water (2x40 mL) and brine (2x40 mL). The organic phase was dried (MgSO<sub>4</sub>) and the solvents were removed under reduced pressure to afford a crude product that was purified by flash chromatography over silica eluting with EtOAc/Hexanes to yield pure amide **3.2a-n**.

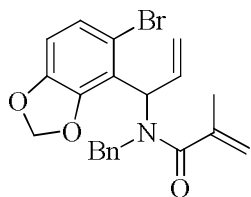


***N*-benzyl-*N*-(1-(2-bromo-4,5-dimethoxyphenyl)allyl)methacrylamide (**3.2a**).** Treatment of imine **3.1a** (335 mg, 1.00 mmol, 1.0 equiv), methacryloyl chloride (139 mg, 130  $\mu$ L, 1.30 mmol, 1.3 equiv) and tributylvinyltin (386 mg, 1.20 mmol, 1.2 equiv) with CuCl (10 mg, 0.10 mmol, 0.1 equiv) in ACN (4 mL) and DCM (8 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) afforded amide **3.2a** (355 mg, 83%) as a clear heavy oil:  $R_f$  = 0.40 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.17-7.12 (m, 3H), 7.00 (d,  $J$  = 7.3 Hz, 2H), 6.84 (br s, 1H), 6.76 (s, 1H), 6.08 (dt,  $J$  = 5.3 Hz,  $J$  = 1.5 Hz, 1H), 5.99 (ddd,  $J$  = 17.1 Hz,  $J$  = 10.4 Hz,  $J$  = 5.3 Hz, 1H), 5.36 (br s, 1H), 5.26 (br s, 1H), 5.21 (s, 0.5H), 5.19 (s, 1H), 5.17 (s, 0.5H), 4.69 (br s, 1H), 4.43 (br s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.02 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  21.3, 47.8, 56.2, 56.3, 63.0, 113.5, 115.5, 115.7, 115.9, 118.2, 126.8, 127.3 (2C), 128.1 (2C), 129.6, 135.9, 138.0, 140.7,

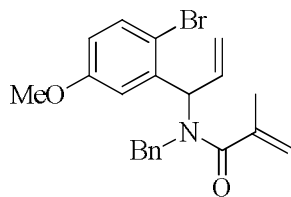
148.3, 149.2, 173.7; IR (cm<sup>-1</sup>) 1647, 1620, 1252; Significant signal broadening of some signals in <sup>1</sup>H and <sup>13</sup>C NMR arises due to hindered rotation about the amide bond. See temperature dependent <sup>1</sup>H NMR spectra for **3.2b**; HRMS (ES<sup>+</sup>) calcd for C<sub>22</sub>H<sub>24</sub>BrNO<sub>3</sub>Na (M+Na)<sup>+</sup> 452.0837, found 452.0835.



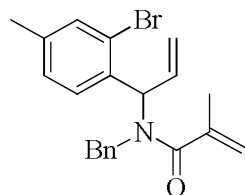
***N*-benzyl-*N*-(1-(6-bromobenzo[d][1,3]dioxol-5-yl)allyl)methacrylamide (**3.2b**).** Treatment of imine **3.1b** (1.38 g, 4.33 mmol, 1.0 equiv), methacryloyl chloride (589 mg, 550 μL, 5.66 mmol, 1.3 equiv) and tributylvinyltin (1.66 g, 5.23 mmol, 1.2 equiv) with CuCl (44 mg, 0.44 mmol, 0.1 equiv) in ACN (16 mL) and DCM (32 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) afforded amide **3.2b** (1.304 g, 73%) as a white solid: mp 100-110 °C; *R*<sub>f</sub> = 0.57 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.16 (br t, *J* = 7.1 Hz, 2H), 7.13 (br d, *J* = 6.7 Hz, 1H), 7.02 (d, *J* = 7.3 Hz, 2H), 6.80 (s, 2H), 6.11 (d, *J* = 4.1 Hz, 1H), 5.99-5.96 (m, 0.7H), 5.94 (d, *J* = 1.4 Hz, 1H), 5.94-5.93 (m, 0.3H), 5.91 (d, *J* = 1.4 Hz, 1H), 5.37 (br s, 1H), 5.26 (s, 1H), 5.18 (t, *J* = 8.2 Hz, 2H), 4.77 (br s, 1H), 4.38 (br s, 1H), 2.01 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 21.4, 48.5, 62.7, 102.0, 110.5, 113.0, 115.6, 116.5, 118.1, 126.7, 127.2 (2C), 128.1 (2C), 128.0, 128.9, 135.9, 138.0, 147.5, 148.0, 173.7; Significant signal broadening of some signals in <sup>1</sup>H and <sup>13</sup>C NMR arises due to hindered rotation about the amide bond. See temperature dependent <sup>1</sup>H NMR spectra for **3.2b**; IR (cm<sup>-1</sup>) 1647, 1618, 1238; HRMS (ES<sup>+</sup>) calcd for C<sub>21</sub>H<sub>20</sub>BrNO<sub>3</sub>Na (M+Na)<sup>+</sup> 436.0524, found 436.0516.



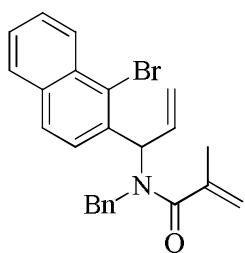
***N*-benzyl-*N*-(1-(5-bromobenzo[d][1,3]dioxol-4-yl)allyl)methacrylamide (**3.2c**).** Treatment of imine **3.1c** (504 mg, 1.58 mmol, 1.0 equiv), methacryloyl chloride (214 mg, 200  $\mu$ L, 2.06 mmol, 1.3 equiv) and tributylvinyltin (602 mg, 1.90 mmol, 1.2 equiv) with CuCl (16 mg, 0.16 mmol, 0.1 equiv) in ACN (6 mL) and DCM (12 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) afforded amide **3.2c** (484 mg, 74%) as a light yellow heavy oil:  $R_f$  = 0.53 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.16 (t,  $J$  = 7.2 Hz, 2H), 7.09 (t,  $J$  = 7.0 Hz, 1H), 7.03 (d,  $J$  = 7.4 Hz, 2H), 6.93 (d,  $J$  = 8.0 Hz, 1H), 6.47 (d,  $J$  = 8.3 Hz, 1H), 6.31 (br s, 1H), 6.11 (ddd,  $J$  = 17.1 Hz,  $J$  = 10.4 Hz,  $J$  = 5.6 Hz, 1H), 5.92 (d,  $J$  = 1.5 Hz, 1H), 5.86 (s, 1H), 5.27 (d,  $J$  = 10.0 Hz, 1H), 5.22 (br s, 0.5H), 5.19 (q,  $J$  = 0.7 Hz, 1H), 5.16 (q,  $J$  = 0.7 Hz, 1H), 5.15 (br s, 0.5H), 4.84 (br d,  $J$  = 13.5 Hz, 1H), 4.70 (br,  $J$  = 14.3 Hz, 1H), 1.93 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  21.3, 47.8, 60.6, 101.5, 109.1, 115.5, 116.3, 117.6, 120.8, 126.0, 126.2 (2C), 126.6, 128.1 (2C), 134.3, 138.7, 140.5, 147.2, 147.3, 173.5; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1645, 1620, 933; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{21}\text{H}_{21}\text{BrNO}_3$  ( $\text{M}+\text{H}$ ) $^+$  414.0705, found 414.0706.



***N*-benzyl-*N*-(1-(2-bromo-5-methoxyphenyl)allyl)methacrylamide (**3.2d**).** Treatment of imine **3.1d** (482 mg, 1.58 mmol, 1.0 equiv), methacryloyl chloride (214 mg, 200  $\mu$ L, 2.06 mmol, 1.3 equiv) and tributylvinyltin (603 mg, 1.90 mmol, 1.2 equiv) with CuCl (16 mg, 0.16 mmol, 0.1 equiv) in ACN (6 mL) and DCM (12 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) afforded amide **3.2d** (399 mg, 63%) as a light yellow heavy oil:  $R_f$  = 0.58 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33-7.27 (m, 1H), 7.16-7.12 (m, 3H), 7.02 (d,  $J$  = 7.2 Hz, 2H), 6.85 (d,  $J$  = 3.1 Hz, 1H), 6.61 (dd,  $J$  = 8.7 Hz,  $J$  = 2.7 Hz, 1H), 6.13 (br s, 1H), 5.97 (ddd,  $J$  = 17.2 Hz,  $J$  = 10.4 Hz,  $J$  = 5.4 Hz, 1H), 5.36 (br d,  $J$  = 8.1 Hz, 1H), 5.24 (s, 1H), 5.20 (q,  $J$  = 1.1 Hz, 0.5H), 5.18 (s, 1H), 5.16 (q,  $J$  = 1.0 Hz, 0.5H), 4.69 (br s, 1H), 4.54 (br d,  $J$  = 13.0 Hz, 1H), 3.72 (s, 3H), 1.99 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  21.3, 47.3, 55.6, 63.3, 114.8, 115.6, 115.7, 117.0, 118.6, 126.8, 127.3 (2C), 128.1 (2C), 122.8, 135.4, 138.1, 138.9, 140.6, 159.0, 173.8; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1647, 1624, 1281; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{21}\text{H}_{22}\text{BrNO}_2\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  422.0732, found 422.0744.

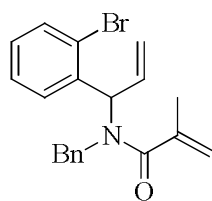


***N*-benzyl-*N*-(1-(2-bromo-4-methylphenyl)allyl)methacrylamide (3.2e).** Treatment of imine **3.1e** (1.23 g, 4.27 mmol, 1.0 equiv), methacryloyl chloride (642 mg, 600  $\mu$ L, 6.17 mmol, 1.3 equiv) and tributylvinyltin (1.64 g, 5.16 mmol, 1.2 equiv) with CuCl (44 mg, 0.44 mmol, 0.1 equiv) in ACN (15 mL) and DCM (30 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) afforded amide **3.2e** (1.213 g, 74%) as a clear oil:  $R_f$  = 0.54 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21 (br s, 1H), 7.18 (d,  $J$  = 7.9 Hz, 1H), 7.13 (br t,  $J$  = 6.7 Hz, 3H), 7.03 (d,  $J$  = 7.9 Hz, 1H), 6.98 (d,  $J$  = 6.9 Hz, 2H), 6.14 (br s, 1H), 5.98 (ddd,  $J$  = 17.2 Hz,  $J$  = 10.5 Hz,  $J$  = 5.3 Hz, 1H), 5.34 (br d,  $J$  = 6.7 Hz, 1H), 5.25 (s, 1H), 5.18 (q,  $J$  = 1.1 Hz, 0.5H), 5.17 (br, 1H), 5.15 (q,  $J$  = 1.1 Hz, 0.5H), 4.65 (br s, 1H), 4.46 (br d,  $J$  = 10.2 Hz, 1H), 2.24 (s, 3H), 1.99 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  20.7, 21.3, 47.1, 63.0, 115.5, 118.1, 125.3, 126.6, 127.3 (2C), 128.0 (2C), 128.3, 130.4, 133.7, 134.8, 135.8, 138.1, 139.9, 140.6, 173.8; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1649, 1620; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{21}\text{H}_{23}\text{BrNO}$  ( $\text{M}+\text{H}$ ) $^+$  384.0963, found 384.0963.



***N*-benzyl-*N*-(1-(1-bromonaphthalen-2-yl)allyl)methacrylamide (3.2f).** Treatment of imine **3.1f** (324 mg, 1.00 mmol, 1.0 equiv), methacryloyl chloride (139 mg, 130  $\mu$ L, 1.30 mmol, 1.3 equiv) and tributylvinyltin (381 mg, 1.20 mmol, 1.2 equiv) with CuCl (10 mg, 0.10 mmol, 0.1

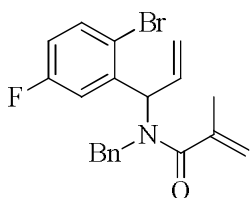
equiv) in ACN (4 mL) and DCM (8 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 3) afforded amide **3.2f** (252 mg, 60%) as a light yellow oil:  $R_f$  = 0.32 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 (d,  $J$  = 8.2 Hz, 1H), 7.77 (d,  $J$  = 8.0 Hz, 1H), 7.74 (d,  $J$  = 8.6 Hz, 1H), 7.56 (td,  $J$  = 8.2 Hz,  $J$  = 1.2 Hz, 1H), 7.51 (td,  $J$  = 8.1 Hz,  $J$  = 1.3 Hz, 1H), 7.44 (d,  $J$  = 8.5 Hz, 1H), 7.06 (br s, 2H), 7.01 (d,  $J$  = 7.3 Hz, 3H), 6.47 (d,  $J$  = 5.4 Hz, 1H), 6.12 (ddd,  $J$  = 16.8 Hz,  $J$  = 10.4 Hz,  $J$  = 5.4 Hz, 1H), 5.36 (d,  $J$  = 10.0 Hz, 1H), 5.23 (s, 1H), 5.18 (q,  $J$  = 1.0 Hz, 1.5H), 5.14 (q,  $J$  = 1.1 Hz, 0.5H), 4.70 (d,  $J$  = 12.6 Hz, 1H), 4.63 (d,  $J$  = 15.7 Hz, 1H), 1.97 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  21.2, 31.1, 64.0, 115.6, 118.5, 126.0, 126.8, 126.8, 127.1, 127.1 (2C), 127.7 (2C), 127.7, 128.0, 128.0, 128.1, 132.4, 134.1, 135.6, 136.1, 138.1, 140.7, 173.8; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1647, 1624; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{24}\text{H}_{22}\text{BrNONa}$  ( $\text{M}+\text{Na}$ ) $^+$  442.0782, found 442.0784.



**N-benzyl-N-(1-(2-bromophenyl)allyl)methacrylamide (3.2g).** Treatment of imine **3.1g** (837 mg, 3.05 mmol, 1.0 equiv), methacryloyl chloride (417 mg, 390  $\mu\text{L}$ , 4.01 mmol, 1.3 equiv) and tributylvinyltin (1.159 g, 3.66 mmol, 1.2 equiv) with CuCl (31 mg, 0.31 mmol, 0.1 equiv) in ACN (12 mL) and DCM (24 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 5) afforded amide **3.2g** (809 mg, 72%) as a yellow oil:  $R_f$  = 0.59 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40

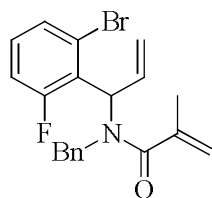


(br s, 1H), 7.32 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 7.24 (dt,  $J = 7.5$  Hz,  $J = 1.1$  Hz, 1H), 7.15-7.09 (m, 3H), 7.05 (t,  $J = 7.5$  Hz, 1H), 6.98 (d,  $J = 7.0$  Hz, 2H), 6.19 (br, 1H), 6.00 (ddd,  $J = 17.2$  Hz,  $J = 10.4$  Hz,  $J = 5.3$  Hz, 1H), 5.36 (d,  $J = 8.2$  Hz, 1H), 5.24 (s, 1H), 5.20 (q,  $J = 0.7$  Hz, 0.5H), 5.18 (s, 1H), 5.16 (q,  $J = 0.7$  Hz, 0.5H), 4.60 (br, 1H), 4.50 (d,  $J = 12.3$  Hz, 1H), 1.99 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  21.3, 47.8, 63.1, 115.5, 118.4, 125.5, 126.7, 127.2 (2C), 127.5, 128.1 (2C), 129.6, 130.7, 133.6, 135.6, 138.0, 138.1, 140.6, 173.8; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1647, 1622; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{20}\text{H}_{21}\text{BrNO}$  ( $\text{M}+\text{H}$ ) $^+$  370.0807, found 370.0811.



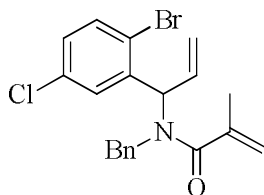
***N*-benzyl-*N*-(1-(2-bromo-5-fluorophenyl)allyl)methacrylamide (3.2h).** Treatment of imine **3.1h** (288 mg, 0.99 mmol, 1.0 equiv), methacryloyl chloride (134 mg, 125  $\mu\text{L}$ , 1.29 mmol, 1.3 equiv) and tributylvinyltin (381 mg, 1.20 mmol, 1.2 equiv) with  $\text{CuCl}$  (10 mg, 0.10 mmol, 0.1 equiv) in ACN (4 mL) and DCM (8 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 5) afforded amide **3.2h** (193 mg, 50%) as a yellow oil:  $R_f = 0.61$  (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-7.27 (m, 1H), 7.09-7.23 (m, 3H), 7.04 (dd,  $J = 9.6$  Hz,  $J = 3.0$  Hz, 1H), 7.01 (d,  $J = 7.4$  Hz, 2H), 6.78 (dt,  $J = 8.4$  Hz,  $J = 2.9$  Hz, 1H), 6.13 (d,  $J = 5.0$  Hz, 1H), 5.96 (ddd,  $J = 17.2$  Hz,  $J = 10.4$  Hz,  $J = 5.3$  Hz, 1H), 5.39 (br d,  $J = 6.8$  Hz, 1H), 5.24 (s, 1H), 5.21-5.17 (m, 2H), 4.72 (br s, 1H), 4.48 (br s, 1H), 2.00 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  21.3, 48.2, 62.7,

115.7, 116.7 (d,  $J = 21.3$  Hz), 118.0 ( $J = 23.8$  Hz), 119.0, 119.4 ( $J = 2.5$  Hz), 126.9, 127.2 (2C), 128.0 (d,  $J = 82.5$  Hz), 128.2 (2C), 134.4 (d,  $J = 8.8$  Hz), 134.8, 137.8, 140.2, 162.0 (d,  $J = 246.3$  Hz), 173.7; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1647, 1624; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{20}\text{H}_{20}\text{BrFNO}$  ( $\text{M}+\text{H}$ ) $^+$  388.0712, found 388.0719.

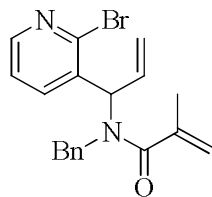


***N*-benzyl-*N*-(1-(2-bromo-6-fluorophenyl)allyl)methacrylamide (3.2i).** Treatment of imine **3.1i** (462 mg, 1.58 mmol, 1.0 equiv), methacryloyl chloride (214 mg, 200  $\mu\text{L}$ , 2.06 mmol, 1.3 equiv) and tributylvinyltin (603 mg, 1.90 mmol, 1.2 equiv) with CuCl (16 mg, 0.16 mmol, 0.1 equiv) in ACN (6 mL) and DCM (12 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 5) afforded amide **3.2i** (473 mg, 77%) as a yellow oil:  $R_f = 0.68$  (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 (d,  $J = 7.8$  Hz, 1H), 7.20 (t,  $J = 7.2$  Hz, 2H), 7.12 (t,  $J = 7.1$  Hz, 1H), 7.08 (d,  $J = 7.4$  Hz, 2H), 7.01 (dt,  $J = 8.2$  Hz,  $J = 5.8$  Hz, 1H), 6.90 (ddd,  $J = 11.0$  Hz,  $J = 8.5$  Hz,  $J = 0.8$  Hz, 1H), 6.41 (br s, 1H), 6.13-6.06 (m, 1H), 5.22 (d,  $J = 10.3$  Hz, 1H), 5.13-5.09 (m, 3H), 4.88-4.80 (m, 2H), 1.83 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  20.8, 49.2, 60.7, 115.5, 115.7 (d,  $J = 23.8$  Hz), 118.2, 125.8 (d,  $J = 6.3$  Hz), 126.2 (2C), 126.7, 127.3, 128.3 (2C), 128.7, 129.2 (d,  $J = 3.8$  Hz), 130.0 (d,  $J = 8.8$  Hz), 133.4, 139.7 (d,  $J = 196.3$  Hz), 161.6 (d,  $J = 250.0$  Hz), 173.7; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the

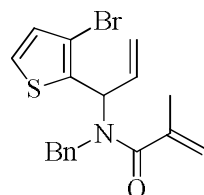
amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1649, 1624; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{20}\text{H}_{20}\text{BrFNO}$  ( $\text{M}+\text{H}$ ) $^+$  388.0712, found 388.0704.



***N*-benzyl-*N*-(1-(2-bromo-5-chlorophenyl)allyl)methacrylamide (3.2j).** Treatment of imine **3.1j** (1.285 g, 4.16 mmol, 1.0 equiv), methacryloyl chloride (567 mg, 530  $\mu\text{L}$ , 5.45 mmol, 1.3 equiv) and tributylvinyltin (1.587 g, 5.01 mmol, 1.2 equiv) with CuCl (41 mg, 0.41 mmol, 0.1 equiv) in ACN (16 mL) and DCM (32 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 5) afforded amide **3.2j** (959 mg, 57%) as a light yellow oil:  $R_f$  = 0.63 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33-7.28 (m, 1H), 7.25 (d,  $J$  = 2.5 Hz, 1H), 7.16 (d,  $J$  = 6.7 Hz, 2H), 7.12 (d,  $J$  = 6.0 Hz, 1H), 6.99 (d,  $J$  = 6.9 Hz, 3H), 6.15 (br d,  $J$  = 4.0 Hz, 1H), 5.96 (ddd,  $J$  = 17.2 Hz,  $J$  = 10.5 Hz,  $J$  = 5.3 Hz, 1H), 5.41 (br s, 1H), 5.25 (s, 1H), 5.23 (s, 0.5H), 5.19 (s, 1.5H), 4.75 (br s, 1H), 4.44 (br s, 1H), 2.01 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  21.3, 48.2, 62.6, 115.7, 119.0, 123.3, 126.9, 127.3 (2C), 128.2, 129.6, 130.8, 133.6, 134.2 (2C), 134.7, 137.8, 139.8, 140.4, 173.7; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1647, 1624; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{20}\text{H}_{19}\text{BrClINONa}$  ( $\text{M}+\text{Na}$ ) $^+$  426.0236, found 426.0239.

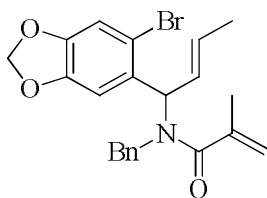


***N*-benzyl-*N*-(1-(2-bromopyridin-3-yl)allyl)methacrylamide (3.2k).** Treatment of imine **3.1k** (518 mg, 1.88 mmol, 1.0 equiv), methacryloyl chloride (257 mg, 240  $\mu$ L, 2.47 mmol, 1.3 equiv) and tributylvinyltin (716 mg, 2.26 mmol, 1.2 equiv) with CuCl (19 mg, 0.19 mmol, 0.1 equiv) in ACN (7 mL) and DCM (14 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 3) afforded amide **3.2k** (431 mg, 62%) as a light yellow oil:  $R_f$  = 0.39 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.17 (d,  $J$  = 3.0 Hz, 1H), 7.65 (d,  $J$  = 7.2 Hz, 1H), 7.17 (dd,  $J$  = 7.7 Hz,  $J$  = 4.7 Hz, 4H), 7.01 (d,  $J$  = 6.4 Hz, 2H), 6.05 – 5.99 (m, 2H), 5.38 (s, 1H), 5.23 (d,  $J$  = 16.9 Hz, 2H), 5.17 (d,  $J$  = 16.9 Hz, 1H), 4.79 (s, 1H), 4.51 – 4.46 (m, 1H), 2.01 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  21.2, 49.8, 62.2, 116.0 (2C), 119.2, 122.7 (2C), 127.2 (2C), 128.4, 134.4, 135.8, 137.4, 139.1, 140.4, 144.8, 149.3, 173.7; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1655, 1618; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{19}\text{H}_{19}\text{BrN}_2\text{ONa}$  ( $\text{M}+\text{Na}$ ) $^+$  393.0578, found 39.0539.



***N*-benzyl-*N*-(1-(3-bromothiophen-2-yl)allyl)methacrylamide (3.2l).** Treatment of imine **3.1l** (417 mg, 1.50 mmol, 1.0 equiv), methacryloyl chloride (203 mg, 190  $\mu$ L, 1.95 mmol, 1.3 equiv)

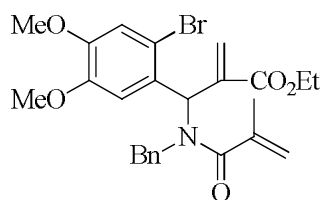
and tributylvinyltin (574 mg, 1.81 mmol, 1.2 equiv) with CuCl (15 mg, 0.16 mmol, 0.1 equiv) in ACN (6 mL) and DCM (12 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 5) afforded amide **3.2l** (443 mg, 78%) as a light yellow oil:  $R_f$  = 0.61 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.22-7.16 (m, 4H), 7.09 (t,  $J$  = 6.9 Hz, 2H), 6.79 (dd,  $J$  = 40.8 Hz,  $J$  = 4.5 Hz, 1H), 6.11-6.04 (m, 2H), 5.30 (br s, 1H), 5.23-5.18 (m, 3H), 4.72 (t,  $J$  = 15.1 Hz, 1H), 4.54 (dd,  $J$  = 21.8 Hz,  $J$  = 16.1 Hz, 1H), 2.01 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  20.9, 47.2, 58.6, 115.6, 115.8, 118.4, 118.5, 125.2, 126.1, 127.1 (2C), 127.2 (2C), 128.3, 135.2, 135.3, 137.8, 173.5; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1647, 1624; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{18}\text{H}_{19}\text{BrNOS}$  ( $\text{M}+\text{H}$ ) $^+$  376.0371, found 376.0364.



**(E)-N-benzyl-N-(1-(2-bromo-4,5-dimethoxyphenyl)but-2-en-1-yl)methacrylamide (3.2m).**

Treatment of imine **3.1b** (477 mg, 1.50 mmol, 1.0 equiv), methacryloyl chloride (203 mg, 190  $\mu\text{L}$ , 1.30 mmol, 1.3 equiv) and (E)-tributyl(prop-1-en-1-yl)stannane (595 mg, 1.80 mmol, 1.2 equiv) with CuCl (15 mg, 0.15 mmol, 0.1 equiv) in ACN (4 mL) and DCM (8 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) afforded amide **3.2m** (482 mg, 75%) as a clear heavy oil:  $R_f$  = 0.57 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.22 (t,  $J$  = 7.0 Hz, 2H), 7.18 (d,  $J$  = 7.1 Hz, 1H), 7.08 (d,  $J$  = 7.1 Hz, 2H), 6.90 (s, 1H), 6.82 (s, 1H), 6.19 (d,  $J$  = 5.5 Hz, 1H), 5.96 (q,  $J$  =

1.4 Hz, 2H), 5.62 (d,  $J = 5.9$  Hz, 2H), 5.23 (s, 1H), 5.21 (s, 1H), 4.70 (d,  $J = 15.8$  Hz, 1H), 4.36 (d,  $J = 15.8$  Hz, 1H), 1.98 (s, 3H), 1.49 (d,  $J = 4.3$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  13.6, 21.0, 31.1, 43.2, 102.0, 110.3, 113.1, 115.7, 115.9, 126.9, 127.4, 127.5 (2C), 128.3 (2C), 128.5, 128.8, 132.3, 138.5, 147.5, 147.9, 173.5; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1651, 1622; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{22}\text{H}_{22}\text{BrNO}_3\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  450.0681, found 450.0675.

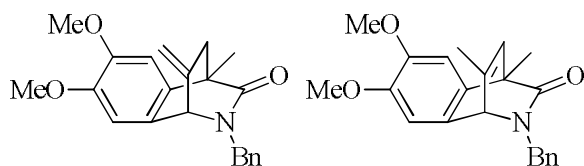


**ethyl 2-((*N*-benzylmethacrylamido)(2-bromo-4,5-dimethoxyphenyl)methyl)acrylate (**3.2n**).**

Treatment of imine **3.1a** (606 mg, 1.81 mmol, 1.0 equiv), methacryloyl chloride (230  $\mu\text{L}$ , 2.30 mmol, 1.3 equiv) and ethyl 2-(tributylstannyl)acrylate (861 mg, 2.21 mmol, 1.2 equiv) with  $\text{CuCl}$  (21 mg, 0.21 mmol, 0.1 equiv) in ACN (8 mL) and DCM (16 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) afforded amide **3.2n** (655 mg, 72%) as a clear heavy oil:  $R_f = 0.40$  (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.16 (t,  $J = 7.1$  Hz, 2H), 7.10 (t,  $J = 6.5$  Hz, 1H), 7.04 (d,  $J = 6.7$  Hz, 2H), 6.85 (s, 1H), 6.69 (s, 1H), 6.45 (d,  $J = 28.9$  Hz, 2H), 5.45 (s, 1H), 5.15 (s, 1H), 4.99 (s, 1H), 4.70 (s, 2H), 4.06 – 3.90 (m, 2H), 3.79 (s, 3H), 3.66 (s, 3H), 2.05 (s, 3H), 1.12 (dt,  $J = 7.0$  Hz,  $J = 1.0$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 20.9, 47.1, 56.1, 56.2, 61.2, 62.7, 111.8, 114.5, 115.4, 116.0, 126.7, 127.7 (2C), 128.1 (2C), 128.8, 130.1, 137.7, 140.1, 140.4, 148.6, 149.0, 165.3, 174.8; Significant signal broadening of some signals in  $^1\text{H}$  and

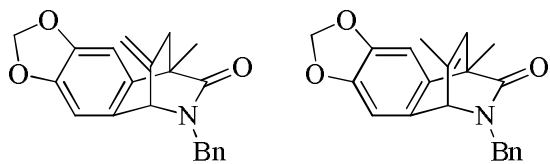
$^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 1718, 1649, 1628; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{25}\text{H}_{28}\text{BrNO}_5\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  524.1049, found 524.1038.

**General protocol for the preparation of azabicyclooctanes 3.4a-m and 3.4a-m'.** A solution of amide **3.2a-m** (1.0 equiv) in DMF (0.12 M) was injected into a reaction vessel containing the solid reagents including sodium carbonate (1.0 equiv), tetrabutylammonium chloride (1.0 equiv) and palladium acetate (0.1 equiv). In situations when the imine was a solid, it was added along with the other solid reagents. The reaction mixture was then stirred at 80 °C for 18-26 h. After cooling to room temperature the solution was diluted with water (10 mL) and extracted with ethyl acetate (3x30 mL). The combined organic phase was washed with water (2x40 mL) and brine (2x40 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography over silica eluting with ethyl EtOAc/hexane to yield an isomeric mixture of azabicyclooctanes **3.4a-m** and **3.4a-m'**.



**(1S,4R)-10-benzyl-6,7-dimethoxy-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.4a) and (1S,4R)-10-benzyl-6,7-dimethoxy-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.4a').** Treatment of amide **3.2a** (300 mg, 0.70 mmol, 1.0 equiv), sodium carbonate (74 mg, 0.70 mmol, 1.0 equiv) and tetrabutylammonium chloride (200 mg, 0.72 mmol, 1.0 equiv) with palladium acetate (18 mg,

0.082 mmol, 0.1 equiv) in DMF (8 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) afforded azabicyclooctanes **3.4a** and **3.4a'** (166 mg, 68%) as a light yellow oil, as a 1.3 : 1.0 mixture of **3.4a** : **3.4a'** (by  $^1\text{H}$  NMR):  $R_f$  = 0.31 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.23 (m, 3H), 7.10 (dd,  $J$  = 7.8 Hz,  $J$  = 2.2 Hz, 1H), 7.07 (dd,  $J$  = 7.6 Hz,  $J$  = 2.0 Hz, 1H), 6.87 (s, 0.44H), 6.82 (s, 0.56H), 6.66 (s, 0.44H), 6.56 (s, 0.56H), 6.05 (p,  $J$  = 1.9 Hz, 0.44H), 4.88 (t,  $J$  = 2.2 Hz, 0.56H), 4.83 (d,  $J$  = 15.3 Hz, 0.56H), 4.73 (d,  $J$  = 15 Hz, 0.44H), 4.71 (t,  $J$  = 1.9 Hz, 0.56H), 4.53 (s, 0.56H), 4.48 (d,  $J$  = 2.1 Hz, 0.44H), 4.38 (d,  $J$  = 15.3 Hz, 0.56H), 4.22 (d,  $J$  = 15.1 Hz, 0.44H), 3.90 (s, 1.68H), 3.88 (s, 1.32H), 3.80 (s, 1.32H), 3.79 (s, 1.68H), 2.60 (dt,  $J$  = 16.2 Hz,  $J$  = 2.2 Hz, 0.56H), 2.19 (dt,  $J$  = 16.2 Hz,  $J$  = 2.1 Hz, 0.56H), 1.84 (s, 1.32H), 1.71 (s, 1.68H) 1.65 (d,  $J$  = 1.8 Hz, 1.32H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  [14.2], 16.1, [18.1], 38.8, 47.1, 48.3, [49.2], [53.8], 56.3, 56.4, [56.4], [56.5], [63.7], 64.4, 106.3, 106.5, [106.6], [107.1], 107.6, 127.5, [127.7], 128.1 (2C), [128.4 (2C)], 128.6 (2C), [128.7 (2C)], 131.9, [133.5], 134.8, [135.3], 136.9, [137.1], [137.4], 143.7, [146.3], [146.7], 147.2, [147.8], 148.6, 174.9, [175.0]; Values in brackets are for the minor isomer **3.4a'**; IR ( $\text{cm}^{-1}$ ) 1668, 1607, 1290, 1059, 733; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{22}\text{H}_{24}\text{NO}_3$  ( $\text{M}+\text{H}$ ) $^+$  350.1756, found 350.1758.



**(5*S*,8*R*)-11-benzyl-8-methyl-6-methylene-5,6,7,8-tetrahydro-5,8-(epiminomethano)naphtho[2,3-d][1,3]dioxol-10-one (3.4b) and (5*S*,8*R*)-11-benzyl-6,8-dimethyl-5,8-dihydro-5,8-(epiminomethano)naphtho[2,3-d][1,3]dioxol-10-one (3.4b').**

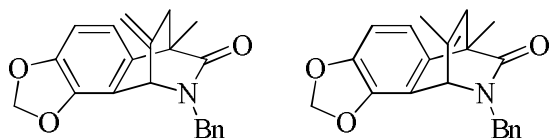
Treatment of amide **3.2b** (1.521 g, 3.67 mmol, 1.0 equiv), sodium carbonate (390 mg, 3.68



mmol, 1.0 equiv) and tetrabutylammonium chloride (1.012 g, 3.67 mmol, 1.0 equiv) with palladium acetate (83 mg, 0.37 mmol, 0.1 equiv) in DMF (30 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) afforded **3.4b** and **3.4b'** (1.103 g, 90%) as a clear oil, as a 1.5 : 1.0 mixture of **3.4b** : **3.4b'** (by  $^1\text{H}$  NMR):  $R_f$  = 0.52 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33-7.24 (m, 3H), 7.13-7.08 (m, 2H), 6.83 (s, 0.4H), 6.80 (s, 0.6H), 6.63 (s, 0.4H), 6.52 (s, 0.6H), 6.02 (p,  $J$  = 2.0 Hz, 0.4H), 5.95 (d,  $J$  = 2.0 Hz, 0.6H), 5.93 (d,  $J$  = 2.0 Hz, 0.4H), 5.91 (d,  $J$  = 1.0 Hz, 0.6H), 5.90 (d,  $J$  = 1.5 Hz, 0.4H), 4.87 (t,  $J$  = 2.0 Hz, 0.6H), 4.79 (d,  $J$  = 15.3 Hz, 0.6H), 4.78 (d,  $J$  = 14.9 Hz, 0.4H), 4.70 (t,  $J$  = 2.0 Hz, 0.6H), 4.50 (s, 0.6H), 4.44 (d,  $J$  = 2.0 Hz, 0.4H), 4.37 (d,  $J$  = 15.0 Hz, 0.6H), 4.13 (d,  $J$  = 15.0 Hz, 0.4H), 2.51 (dt,  $J$  = 16.5 Hz,  $J$  = 2.0 Hz, 0.6H), 2.18 (dt,  $J$  = 16.0 Hz,  $J$  = 2.0 Hz, 0.6H), 1.80 (s, 1.2H), 1.67 (s, 1.8H) 1.61 (d,  $J$  = 1.4 Hz, 1.2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  [14.3], 16.2, [18.0], 38.7, 47.3, 48.3, [49.2], [54.0], [63.8], 64.5, 101.2, [101.3], 103.8, [104.08], 104.12, [104.2], 107.8, 127.6, [127.7], 128.1 (2C), [128.3 (2C)], 128.6 (2C), [128.7 (2C)], 133.0, [134.6], 135.2, [136.6], 136.8, [137.1], [139.3], 143.5, [144.8], [145.5], 146.2, [147.27], 147.29, 174.7, [174.9]; Values in brackets are for the minor isomer **3.4b'**; IR ( $\text{cm}^{-1}$ ) 1740, 1682, 1242, 1047; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{21}\text{H}_{19}\text{NO}_3\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  356.1263, found 356.1253.

**Preparation of a single regioisomer of 3.4b:** THF (4 mL) was injected into a reaction vessel containing the solid reagents including amide **3.2b** (142 mg, 0.34 mmol, 1.0 equiv) and tetrakis(triphenylphosphine)palladium (20 mg, 0.02 mmol, 0.05 equiv), followed by neat triethylamine (138 mg, 190  $\mu\text{L}$ , 1.36 mmol, 4.0 equiv). The reaction mixture was stirred at 80  $^\circ\text{C}$  for 23 h, cooled, diluted with 10 mL of water and extracted with ethyl acetate (3x30 mL). The combined organic phase was washed with water (2x40 mL), brine (2x40 mL) and dilute HCl

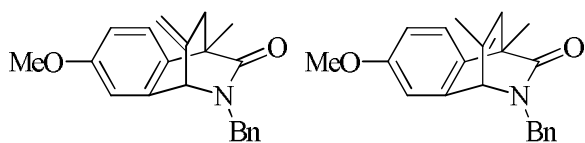
(1x30 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) to afford azabicyclooctanes **3.4b** (102mg, 90%) as white solid, mp 120-124 °C; *R<sub>f</sub>* = 0.52 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.29-7.23 (m, 3H), 7.10 (d, *J* = 1.9, 1H), 7.08 (d, *J* = 1.3, 1H), 6.80 (s, 1H), 6.52 (s, 1H), 5.95 (d, *J* = 1.5 Hz, 1H), 5.91 (d, *J* = 1.5 Hz, 1H), 4.87 (t, *J* = 2.3 Hz, 1H), 4.79 (d, *J* = 15.3 Hz, 1H), 4.70 (t, *J* = 1.9 Hz, 1H), 4.50 (s, 1H), 4.38 (d, *J* = 15.3 Hz, 1H), 2.57 (dt, *J* = 16.1 Hz, *J* = 2.2 Hz, 1H), 2.16 (dt, *J* = 16.2 Hz, *J* = 2.2 Hz, 1H), 1.67 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 16.2, 38.7, 47.3, 48.3, 64.5, 101.2, 103.8, 104.1, 107.8, 127.6, 128.1 (2C), 128.6 (2C), 133.0, 135.2, 136.8, 143.5, 146.2, 147.3, 174.7; IR (cm<sup>-1</sup>) 1666, 1479, 910, 735; HRMS (ES<sup>+</sup>) calcd for C<sub>21</sub>H<sub>19</sub>NO<sub>3</sub>Na (M+Na)<sup>+</sup> 356.1263, found 356.1262.



**(6*R*,9*S*)-10-benzyl-6-methyl-8-methylene-6,7,8,9-tetrahydro-9,6-(epiminomethano)naphtho[1,2-d][1,3]dioxol-11-one (3.4c) and (6*R*,9*S*)-10-benzyl-6,8-dimethyl-6,9-dihydro-9,6-(epiminomethano)naphtho[1,2-d][1,3]dioxol-11-one (3.4c').**

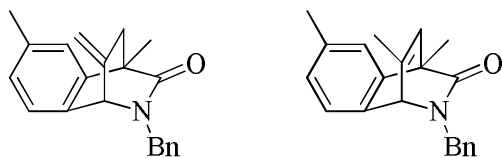
Treatment of amide **3.2c** (104 mg, 0.25 mmol, 1.0 equiv), sodium carbonate (27 mg, 0.25 mmol, 1.0 equiv) and tetrabutylammonium chloride (69 mg, 0.25 mmol, 1.0 equiv) with palladium acetate (6 mg, 0.025 mmol, 0.1 equiv) in DMF (4 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 4) afforded azabicyclooctanes **3.4c** and **3.4c'** (67 mg, 80%) as a clear oil, as a 1.1 : 1.0 mixture of **3.4c** : **3.4c'** (by <sup>1</sup>H NMR); *R<sub>f</sub>* = 0.33 (EtOAc/hexane 1 : 2.3); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ

7.29 (d,  $J = 1.7$  Hz, 0.33H), 7.28 (d,  $J = 1.9$  Hz, 0.67H), 7.25 (t,  $J = 1.9$  Hz, 0.33H), 7.17 (t,  $J = 7.2$  Hz, 0.66H), 7.14 – 7.11 (m,  $J = 6.2, 4.5, 1.9$  Hz, 2.01H), 7.03 (d,  $J = 7.4$  Hz, 0.67H), 6.93 (d,  $J = 8.0$  Hz, 0.33H), 6.73 – 6.68 (m, 1H), 6.51 (d,  $J = 7.7$  Hz, 0.67H), 6.47 (d,  $J = 8.3$  Hz, 0.33H), 6.11 (ddd,  $J = 17.1$  Hz,  $J = 10.3$  Hz,  $J = 5.6$  Hz, 0.66H), 6.03 (p,  $J = 1.8$  Hz, 0.67H), 5.92 (d,  $J = 1.4$  Hz, 0.33H), 5.90 (d,  $J = 1.5$  Hz, 0.33H), 5.88 (d,  $J = 1.5$  Hz, 0.67H), 5.82 (d,  $J = 1.4$  Hz, 0.67H), 4.83 (s, 0.33H), 4.79 (s, 0.33H), 4.77 (d,  $J = 2.1$  Hz, 0.67H), 4.76 (s, 0.34H), 4.74 (s, 0.16H), 4.71 (s, 0.17H), 4.48 (d,  $J = 15.1$  Hz, 0.33H), 4.20 (d,  $J = 14.9$  Hz, 0.67H), 2.60 (dt,  $J = 16.3$  Hz,  $J = 2.2$  Hz, 0.33H), 2.21 (dt,  $J = 16.0$  Hz,  $J = 2.2$  Hz, 0.33H), 1.80 (s, 2.01H), 1.67 (s, 0.99H), 1.64 (d,  $J = 1.8$  Hz, 2.01H); 14.5, [16.3], 18.1, 38.9, [47.4], [48.5], 49.2, [53.8], 57.9, [58.6], 101.3, [101.5], 104.4, [106.8], [108.4], [109.1], 114.1, 115.0, [115.5], 116.3, [122.6], [126.0], 126.2, [127.5], 127.7, [128.2 (2C)], 128.5 (2C), [128.6 (2C)], 128.7 (2C), 135.1, 137.0, [139.3], [140.8], [142.7], 145.8, 146.0, [173.5], 175.0; IR ( $\text{cm}^{-1}$ ) 1678, 1651, 1043; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{21}\text{H}_{19}\text{NO}_3\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  356.1263, found 356.1253.



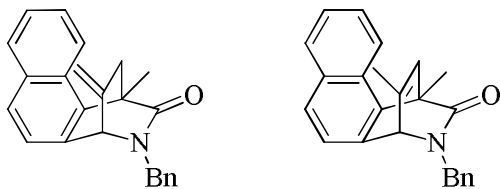
**(1*S*,4*R*)-10-benzyl-7-methoxy-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.4d) and (1*S*,4*R*)-10-benzyl-7-methoxy-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.4d').** Treatment of amide **3.2d** (103 mg, 0.26 mmol, 1.0 equiv), sodium carbonate (28 mg, 0.26 mmol, 1.0 equiv) and tetrabutylammonium chloride (72 mg, 0.26 mmol, 1.0 equiv) with palladium acetate (6 mg, 0.027 mmol, 0.1 equiv) in DMF (4 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 5) afforded

azabicyclooctanes **3.4d** and **3.4d'** (54 mg, 65%) as a clear oil, as a 1.3 : 1.0 mixture of **3.4d** : **3.4d'** (by  $^1\text{H}$  NMR):  $R_f$  = 0.31 (EtOAc/hexane 1 : 2.3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32-7.23 (m, 3H), 7.18 (d,  $J$  = 8.3 Hz, 0.56H), 7.15 (d,  $J$  = 8.2 Hz, 0.44H), 7.13 (dd,  $J$  = 8.1 Hz,  $J$  = 1.8 Hz, 0.88H), 7.10 (dd,  $J$  = 7.8 Hz,  $J$  = 2.1 Hz, 1.12H), 6.79 (dd,  $J$  = 8.4 Hz,  $J$  = 2.6 Hz, 0.56H), 6.69 (d,  $J$  = 2.5 Hz, 0.44H), 6.61 (d,  $J$  = 2.5 Hz, 0.22H), 6.59 (d,  $J$  = 2.5 Hz, 0.78H), 6.04 (p,  $J$  = 1.9 Hz, 0.44H), 4.90 (t,  $J$  = 2.3 Hz, 0.56H), 4.82 (d,  $J$  = 15.1 Hz, 0.44H), 4.76 (d,  $J$  = 15.3 Hz, 0.56H), 4.73 (t,  $J$  = 1.9 Hz, 0.56H), 4.56 (s, 0.56H), 4.48 (d,  $J$  = 2.1 Hz, 0.44H), 4.44 (d,  $J$  = 15.3 Hz, 0.56H), 4.11 (d,  $J$  = 15.1 Hz, 0.44H), 3.76 (s, 1.32H), 3.75 (s, 1.68H), 2.60 (dt,  $J$  = 16.2 Hz,  $J$  = 2.2 Hz, 0.56H), 2.19 (dt,  $J$  = 16.3 Hz,  $J$  = 2.2 Hz, 0.56H), 1.83 (s, 1.32H), 1.70 (s, 1.68H) 1.62 (d,  $J$  = 1.8 Hz, 1.32H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  [14.1], 15.9, [18.0], 38.9, 46.7, 48.3, [49.1], [53.3], 55.5, [56.6], [63.9], 64.8, 108.4, 108.6, [109.1], [109.7], 112.3, [121.8], 123.1, 127.5, [127.7], 128.1 (2C), [128.4 (2C)], 128.6 (2C), [128.7 (2C)], [133.4], 135.0, 136.7, [136.9], [137.2], 140.6, 143.5, [144.0], [146.4], [157.6], 158.7, [175.0], 175.1; Values in brackets are for the minor isomer **3.4d'**; IR ( $\text{cm}^{-1}$ ) 1612, 1612, 1240, 1028; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{21}\text{H}_{21}\text{NO}_2\text{Na}$  ( $\text{M}+\text{H}$ ) $^+$  342.1470, found 342.1466.



**(1S,4R)-10-benzyl-4,6-dimethyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.4e) and (1S,4R)-10-benzyl-2,4,6-trimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.4e').** Treatment of amide **3.2e** (239 mg, 0.62 mmol, 1.0 equiv), sodium carbonate (69 mg, 0.65 mmol, 1.0 equiv) and tetrabutylammonium chloride (175 mg, 0.63 mmol, 1.0 equiv) with palladium acetate (16 mg,

0.069 mmol, 0.1 equiv) in DMF (7 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 9) afforded azabicyclooctanes **3.4e** and **3.4e'** (146 mg, 77%) as a light yellow oil, as a 1.1 : 1.0 mixture of **3.4e** : **3.4e'** (by  $^1\text{H}$  NMR):  $R_f$  = 0.53 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32-7.23 (m, 3H), 7.14 (s, 0.53H), 7.12 (s, 0.47), 7.11-7.08 (m, 2H), 6.98 (s, 0.47), 6.97 (s, 0.53), 6.91 (d,  $J$  = 7.5 Hz, 0.53H), 6.85 (d,  $J$  = 7.3, 0.47H), 6.02 (p,  $J$  = 1.7 Hz, 0.47H), 4.89 (t,  $J$  = 2.3 Hz, 0.53H), 4.83 (d,  $J$  = 15.1 Hz, 0.47H), 4.76 (d,  $J$  = 15.3 Hz, 0.53H), 4.70 (t,  $J$  = 1.8 Hz, 0.53H), 4.58 (s, 0.53H), 4.51 (d,  $J$  = 2.1 Hz, 0.47H), 4.44 (d,  $J$  = 15.3 Hz, 0.53H), 4.08 (d,  $J$  = 15.1 Hz, 0.47H), 2.60 (dt,  $J$  = 16.2 Hz,  $J$  = 2.2 Hz, 0.53H), 2.37 (s, 1.59H), 2.33 (s, 1.41H), 2.19 (dt,  $J$  = 16.2 Hz,  $J$  = 2.2 Hz, 0.53H), 1.84 (s, 1.41H), 1.71 (s, 1.59H) 1.61 (d,  $J$  = 1.8 Hz, 1.41H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  [14.0], 15.8, [18.0], 21.6, [21.7], 38.7, [47.3], 48.3, 49.1, [54.0], [63.6], 64.4, 107.9, [121.3], 121.8, [122.4], 123.0, [125.4], 127.3, 127.5, [127.7], 128.1 (2C), [128.3 (2C)], 128.6 (2C), [128.7 (2C)], [134.4], 135.7, 136.5, 136.9, [137.2], [137.6], 139.8, 141.2, [143.7], [144.8], [147.0], [174.7], 174.8; Values in brackets are for the minor isomer **3.4e'**; IR ( $\text{cm}^{-1}$ ) 1672, 1495, 700; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{21}\text{H}_{22}\text{NO}$  ( $\text{M}+\text{H}$ ) $^+$  304.1701, found 304.1698.

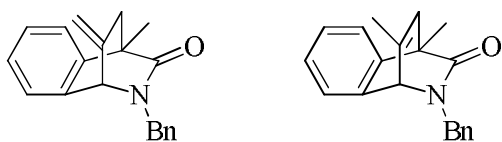


**(1S,4R)-12-benzyl-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-**

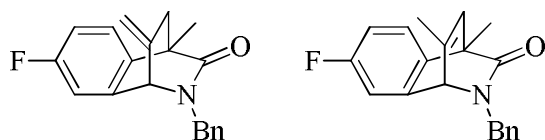
**(epiminomethano)phenanthren-11-one (3.4f) and (1S,4R)-12-benzyl-2,4-dimethyl-1,4-**

**dihydro-1,4-(epiminomethano)phenanthren-11-one (3.4f').** Treatment of amide **3.2f** (235 mg,

0.56 mmol, 1.0 equiv), sodium carbonate (62 mg, 0.58 mmol, 1.0 equiv) and tetrabutylammonium chloride (160 mg, 0.57 mmol, 1.0 equiv) with palladium acetate (13 mg, 0.057 mmol, 0.1 equiv) in DMF (7 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 9) afforded azabicyclooctanes **3.4f** and **3.4f'** (123 mg, 65%) as a yellow solid, as a 2.3 : 1.0 mixture of **3.4f** : **3.4f'** (by  $^1\text{H}$  NMR): mp 110-120 °C;  $R_f$  = 0.52 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.69 (d,  $J$  = 8.8 Hz, 0.7H), 8.65 (d,  $J$  = 8.9 Hz, 0.3H), 7.84 (d,  $J$  = 8.2 Hz, 0.7H), 7.82 (d,  $J$  = 7.7 Hz, 0.3H), 7.68 (d,  $J$  = 8.1 Hz, 0.7H), 7.59 (d,  $J$  = 8.0 Hz, 0.3H), 7.50 (ddd,  $J$  = 8.5 Hz,  $J$  = 6.8 Hz,  $J$  = 1.6 Hz, 0.7H), 7.48-7.42 (m, 1H), 7.37 (ddd,  $J$  = 8.0 Hz,  $J$  = 6.8 Hz,  $J$  = 0.9 Hz, 0.3H), 7.30-7.28 (m, 1H), 7.25-7.22 (m, 2.4H), 7.14-7.12 (m, 1H), 7.11 (s, 0.3H), 7.09-7.07 (m, 1.3), 6.16 (p,  $J$  = 2.0 Hz, 0.3H), 4.97 (t,  $J$  = 2.3 Hz, 0.7H), 4.90 (d,  $J$  = 15.3 Hz, 0.7H), 4.79 (d,  $J$  = 15.1 Hz, 0.3H), 4.75 (t,  $J$  = 1.9 Hz, 0.7H), 4.69 (s, 0.7H), 4.64 (d,  $J$  = 2.3 Hz, 0.3H), 4.41 (d,  $J$  = 15.3 Hz, 0.7H), 4.23 (d,  $J$  = 15.1 Hz, 0.3H), 2.62 (dt,  $J$  = 16.4 Hz,  $J$  = 2.2 Hz, 0.7H), 2.48 (dt,  $J$  = 16.4 Hz,  $J$  = 2.2 Hz, 0.7H), 2.44 (s, 0.9H), 2.32 (s, 2.1H), 1.67 (d,  $J$  = 1.8 Hz, 0.9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  [18.0], [20.1], 21.9, 40.4, 48.3, [49.4], 51.1, [57.8], [64.8], 65.4, 108.1, [121.0], 121.3, [124.0], 124.4, [124.7], 125.1, [126.3], 126.4, [126.9], 127.6, 127.7, 128.1 (2C), [128.4 (2C)], [128.5], 128.6 (2C), [128.8 (2C)], [129.5], 129.7, 130.9, [130.9], [133.2], 134.3, 135.0, 136.8, [137.0], 138.8, [139.6], [142.8], 143.0, 146.8, 174.9, [175.0]; Values in brackets are for the minor isomer **3.4f'**; IR ( $\text{cm}^{-1}$ ) 1668, 1607, 735; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{24}\text{H}_{21}\text{NONa}$  ( $\text{M}+\text{Na}$ ) $^+$  362.1521, found 362.1521.

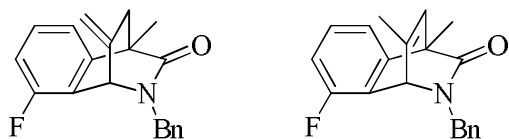


**(1*S*,4*R*)-10-benzyl-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.4g) and (1*S*,4*R*)-10-benzyl-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.4g')**. Treatment of amide **3.2g** (206 mg, 0.56 mmol, 1.0 equiv), sodium carbonate (60 mg, 0.57 mmol, 1.0 equiv) and tetrabutylammonium chloride (155 mg, 0.56 mmol, 1.0 equiv) with palladium acetate (13 mg, 0.056 mmol, 0.1 equiv) in DMF (7 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 9) afforded azabicyclooctanes **3.4g** and **3.4g'** (145 mg, 90%) as a yellow oil, as a 1.0 : 1.0 mixture of **3.4g** : **3.4g'** (by <sup>1</sup>H NMR): *R<sub>f</sub>* = 0.57 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.32-7.28 (m, 3H), 7.26-7.24 (m, 1.5H), 7.18-7.15 (m, 0.5H), 7.14-7.11 (m, 1.5H), 7.09-7.08 (m, 1.5H), 7.06 (dd, *J* = 7.2 Hz, *J* = 1.0 Hz, 0.5H) 7.02 (d, *J* = 7.3, 0.5H), 6.04 (p, *J* = 1.9 Hz, 0.5H), 4.91 (t, *J* = 2.3 Hz, 0.5H), 4.83 (d, *J* = 15.1 Hz, 0.5H), 4.77 (d, *J* = 15.3 Hz, 0.5H), 4.73 (t, *J* = 1.8 Hz, 0.5H), 4.62 (s, 0.5H), 4.54 (d, *J* = 2 Hz, 0.5H), 4.45 (d, *J* = 15.3 Hz, 0.5H), 4.11 (d, *J* = 15.1 Hz, 0.5H), 2.62 (dt, *J* = 16.3 Hz, *J* = 2.1 Hz, 0.5H), 2.21 (dt, *J* = 15.7 Hz, *J* = 2.2 Hz, 0.5H), 1.86 (s, 1.5H), 1.73 (s, 1.5H) 1.62 (d, *J* = 1.8 Hz, 1.5H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ [14.0], 15.8, [18.0], 38.6, 47.4, 48.3, [49.1], [54.1], [63.9], 64.7, 108.3, 121.3, [121.5], 122.0, [122.2], 125.2, [125.9], 126.9, [127.5], 127.7, [127.8], 128.1 (2C), [128.3 (2C)], 128.6 (2C), [128.7 (2C)], [134.5], 136.8, [137.1], [139.3], 141.3, [142.5], [143.5], 144.7, 146.7, 174.6, [174.7]; Values in brackets are for the *endo* isomer **3.4g'**; IR (cm<sup>-1</sup>) 1672, 1605, 748, 733; HRMS (ES<sup>+</sup>) calcd for C<sub>20</sub>H<sub>20</sub>NO (M+H)<sup>+</sup> 290.1545, found 290.1531.



**(1*S*,4*R*)-10-benzyl-7-fluoro-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.4h) and (1*S*,4*R*)-10-benzyl-7-fluoro-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.4h')**. Treatment of amide **3.2h** (245 mg, 0.63 mmol, 1.0 equiv), sodium carbonate (67 mg, 0.63 mmol, 1.0 equiv) and tetrabutylammonium chloride (176 mg, 0.63 mmol, 1.0 equiv) with palladium acetate (14 mg, 0.062 mmol, 0.1 equiv) in DMF (8 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 9) afforded azabicyclooctanes **3.4h** and **3.4h'** (129 mg, 66%) as an orange oil, as a 1.2 : 1.0 mixture of **3.4g** : **3.4h'** (by <sup>1</sup>H NMR): *R*<sub>f</sub> = 0.50 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.30-7.27 (m, 2H), 7.26 (d, *J* = 1.8 Hz, 1H), 7.23 (dd, *J* = 8.4 Hz, *J* = 5.0 Hz, 0.53H), 7.18 (dd, *J* = 9.0 Hz, *J* = 5.0 Hz, 0.47H), 7.11 (dd, *J* = 7.8 Hz, *J* = 2.1 Hz, 0.94H), 7.07 (dd, *J* = 7.7 Hz, *J* = 2.8 Hz, 1.06H), 6.96 (ddd, *J* = 9.2 Hz, *J* = 8.4 Hz, *J* = 2.6 Hz, 0.53H), 6.81-6.77 (m, 0.94H), 6.73 (dd, *J* = 8.0 Hz, *J* = 2.5 Hz, 0.53H), 6.05 (p, *J* = 1.8 Hz, 0.47H), 4.93 (t, *J* = 2.4 Hz, 0.53H), 4.81 (d, *J* = 2.7 Hz, 0.47H), 4.77 (d, *J* = 2.4 Hz, 0.53H), 4.76 (t, *J* = 2.0 Hz, 0.53H), 4.57 (s, 0.53H), 4.50 (d, *J* = 2.1 Hz, 0.47H), 4.41 (d, *J* = 15.2 Hz, 0.53H), 4.15 (d, *J* = 15.1 Hz, 0.47H), 2.61 (dt, *J* = 16.3 Hz, *J* = 2.2 Hz, 0.53H), 2.19 (dt, *J* = 16.2 Hz, *J* = 2.2 Hz, 0.53H), 1.84 (s, 1.41H), 1.71 (s, 1.59H), 1.63 (d, *J* = 1.8 Hz, 1.41H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ [14.1], 16.0, [18.0], 38.5, 47.1, 48.3, [49.2], [53.7], [63.5], 64.3, 109.0, [109.8 (d, *J* = 22.5 Hz)], 110.0 (d, *J* = 23.8 Hz), [111.6 (d, *J* = 21.3 Hz)], 111.1 (d, *J* = 21.3 Hz), [122.2 (d, *J* = 8.8 Hz)], 123.7 (d, *J* = 7.5 Hz), 127.7, [127.85], 128.1 (2C), [128.4 (2C)], 128.7 (2C), [128.8 (2C)], 136.6, [136.88], 136.9 (d, *J* = 2.5 Hz), [140.3 (d, *J* = 2.5 Hz)], [141.1 (d, *J* = 7.5 Hz)], 142.9, 144.6 (d, *J* = 7.5 Hz), [146.4], 160.3 (d, *J* = 113.8 Hz), [162.3 (d, *J* = 113.8 Hz)], 174.4; Values in brackets are for the minor isomer **3.4h'**; IR (cm<sup>-1</sup>) 1672, 1603, 733, 700; HRMS (ES<sup>+</sup>) calcd for C<sub>20</sub>H<sub>19</sub>FNO (M+H)<sup>+</sup> 308.1451, found 308.1446.



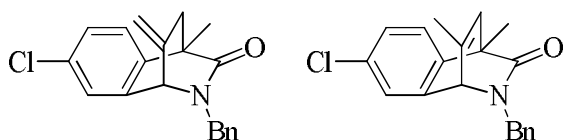


**(1*S*,4*R*)-10-benzyl-8-fluoro-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.4*i*) and (1*S*,4*R*)-10-benzyl-8-fluoro-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.4*i*').** Treatment of amide **3.2i** (96 mg, 0.25 mmol, 1.0 equiv), sodium carbonate (27 mg, 0.26 mmol, 1.0 equiv) and tetrabutylammonium chloride (70 mg, 0.25 mmol, 1.0 equiv) with palladium acetate (6 mg, 0.024 mmol, 0.1 equiv) in DMF (4 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 9) afforded pure azabicyclooctanes **3.4i** (30 mg, 38%) as a light yellow oil, and pure azabicyclooctanes **3.4i'** (41.8 mg, 54%) as a clear oil.

**Analytical data for 3.4i:** mp 65-67 °C;  $R_f$  = 0.5 (EtOAc/hexane 1 : 2.3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.26 (m, 1H), 7.26-7.21 (m, 3H), 7.12-7.10 (m, 2H), 7.07 (d,  $J$  = 7.6 Hz, 1H), 6.89 (dt,  $J$  = 8.5 Hz,  $J$  = 0.8 Hz, 1H), 5.02 (s, 1H), 4.96 (t,  $J$  = 2.4 Hz, 1H), 4.75 (t,  $J$  = 2.0 Hz, 1H), 4.72 (d,  $J$  = 15.1 Hz, 1H), 4.49 (d,  $J$  = 15.1 Hz, 1H), 2.62 (dt,  $J$  = 16.3 Hz,  $J$  = 2.2 Hz, 1H), 2.21 (dt,  $J$  = 16.3 Hz,  $J$  = 2.2 Hz, 1H), 1.72 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  16.0, 38.3, 47.8, 48.6, 57.9, 108.9, 113.9 (d,  $J$  = 20 Hz), 118.0 (d,  $J$  = 3.8 Hz), 125.8 (d,  $J$  = 18.8 Hz), 127.6, 128.1 (2C), 128.7 (2C), 129.1 (d,  $J$  = 7.5 Hz), 136.5, 142.2, 144.4 (d,  $J$  = 5 Hz), 155.8 (d,  $J$  = 246.3 Hz), 174.3; IR ( $\text{cm}^{-1}$ ) 1676, 1622, 700; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{20}\text{H}_{19}\text{FNO}$  ( $\text{M}+\text{H}^+$ ) 308.1451, found 308.1450.

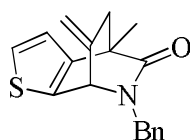
**Analytical data for 3.4i':**  $R_f$  = 0.55 (EtOAc/hexane 1 : 2.3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33-7.28 (m, 3H), 7.14 (dd,  $J$  = 7.9 Hz,  $J$  = 2.0 Hz, 2H), 7.08-7.06 (m, 2H), 6.81-6.77 (m, 1H), 6.05

(p,  $J = 1.9$  Hz, 1H), 4.96 (d,  $J = 2.1$  Hz, 1H), 4.83 (d,  $J = 15.0$  Hz, 1H), 4.12 (d,  $J = 15.0$  Hz, 1H), 1.86 (s, 3H), 1.62 (d,  $J = 1.8$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 17.9, 49.3, 54.5, 57.2, 113.0 (d,  $J = 21.3$  Hz), 117.2 (d,  $J = 2.5$  Hz), 127.4 (d,  $J = 7.5$  Hz), 127.8, 128.4 (2C), 128.5 (d,  $J = 20$  Hz), 128.8 (2C), 134.8, 136.8, 146.4, 148.4 (d,  $J = 5$  Hz), 156.0 (d,  $J = 243.8$  Hz), 174.5; IR ( $\text{cm}^{-1}$ ) 1682, 1622, 700; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{20}\text{H}_{19}\text{FNO}$  ( $\text{M}+\text{H}$ ) $^+$  308.1451, found 308.1442.



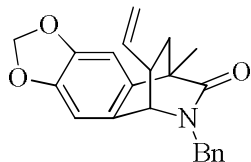
**(1*S*,4*R*)-10-benzyl-7-chloro-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-epiminomethanonaphthalen-9-one (3.4j) and (1*S*,4*R*)-10-benzyl-7-chloro-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.4j')**. Treatment of amide **3.2j** (225 mg, 0.56 mmol, 1.0 equiv), sodium carbonate (60 mg, 0.57 mmol, 1.0 equiv) and tetrabutylammonium chloride (154 mg, 0.55 mmol, 1.0 equiv) with palladium acetate (13 mg, 0.056 mmol, 0.1 equiv) in DMF (7 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 9) afforded azabicyclooctanes **3.4j** and **3.4j'** (145 mg, 80%) as a yellow oil, as a 1.1 : 1.0 mixture of **3.4j** : **3.4j'** (by  $^1\text{H}$  NMR):  $R_f = 0.58$  (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33-7.27 (m, 3H), 7.24 (d,  $J = 2.1$  Hz, 0.48H), 7.21 (d,  $J = 8.1$  Hz, 0.52H), 7.17 (d,  $J = 7.9$  Hz, 0.52H), 7.12-7.07 (m, 2.52H), 7.04 (d,  $J = 2.0$  Hz, 0.48H), 7.00 (d,  $J = 2.0$  Hz, 0.48H), 6.03 (p,  $J = 1.9$  Hz, 0.48H), 4.92 (t,  $J = 2.4$  Hz, 0.52H), 4.81 (d,  $J = 15$  Hz, 0.48H), 4.76-4.75 (m, 0.74H), 4.73, (s, 0.30H), 4.57 (s, 0.52H), 4.49 (d,  $J = 2.0$  Hz, 0.48H), 4.44 (d,  $J = 15.2$  Hz, 0.48H), 4.11 (d,  $J = 14.8$  Hz, 0.52H), 2.61 (dt,  $J = 16.3$  Hz,  $J = 2.2$  Hz, 0.52H), 2.18 (dt,  $J = 16.3$  Hz,  $J = 2.2$  Hz,

0.52H), 1.83 (s, 1.44H), 1.71 (s, 1.56H) 1.61 (d,  $J = 1.8$  Hz 1.44H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  [13.9], 15.8, [18.0], 38.3, 47.2, 48.4, [49.2], [53.9], [63.3], 64.1, 109.0, [122.1], [122.3], [122.4], 123.6, [125.6], 127.71, [127.72], 127.9, 128.1 (2C), [128.4 (2C)], 128.7 (2C), [128.8 (2C)], 133.1, [132.6], 134.5, [136.5], 136.8, [139.8], 140.9, 142.7, [143.3], [144.3], 146.4, 174.19, [174.22]; Values in brackets are for the minor isomer **3.4j'**; IR ( $\text{cm}^{-1}$ ) 1672, 1404, 737, 700; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{20}\text{H}_{19}\text{ClNO}$  ( $\text{M}+\text{H}$ ) $^+$  324.1155, found 324.1144.



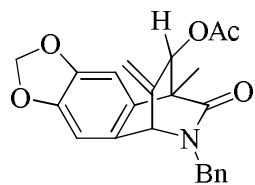
**(4*R*,7*S*)-8-benzyl-4-methyl-6-methylene-4,5,6,7-tetrahydro-7,4-**

**(epiminomethano)benzo[*b*]thiophen-9-one (3.4l).** Treatment of amide **3.2l** (300 mg, 0.80 mmol, 1.0 equiv), sodium carbonate (85 mg, 0.80 mmol, 1.0 equiv) and tetrabutylammonium chloride (223 mg, 0.80 mmol, 1.0 equiv) with palladium acetate (18 mg, 0.080 mmol, 0.1 equiv) in DMF (8 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 9) afforded pure azabicyclooctanes **3.4l** (28 mg, 12%) as a light yellow oil:  $R_f = 0.40$  (EtOAc/hexane 1 : 1.5);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 – 7.31 (d,  $J = 7.5$  Hz, 0.5H), 7.29 – 7.28 (m, 0.5H), 7.28 – 7.27 (m, 1H), 7.24 (t,  $J = 1.0$  Hz, 1H), 7.11 (d,  $J = 1.9$  Hz, 1H), 7.09 (d,  $J = 4.9$  Hz, 2H), 6.92 (d,  $J = 4.9$  Hz, 1H), 4.86 (t,  $J = 2.2$  Hz, 1H), 4.81 (s, 0.5H), 4.79 (s, 1H), 4.78 (s, 0.5H), 4.71 (t,  $J = 1.8$  Hz, 1H), 4.39 (d,  $J = 15.3$  Hz, 1H), 2.56 (dt,  $J = 15.9$  Hz,  $J = 2.0$  Hz, 1H), 2.22 (dt,  $J = 15.9$  Hz,  $J = 2.1$  Hz, 1H), 1.74 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  16.5, 38.7, 47.4, 48.4, 61.0, 107.5, 122.1, 124.2, 127.6, 128.0 (2C), 128.7 (2C), 136.8, 137.0, 143.6, 145.8, 175.3; IR ( $\text{cm}^{-1}$ ) 1674, 1452, 729, 698; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{18}\text{H}_{17}\text{NOSNa}$  ( $\text{M}+\text{Na}$ ) $^+$  318.0929, found 318.0919.



**(5*S*,8*R*)-11-benzyl-8-methyl-6-vinyl-5,6,7,8-tetrahydro-5,8-(epiminomethano)naphtho[2,3-d][1,3]dioxol-10-one (3.4m).** Treatment of amide **3.2m** (112 mg, 0.26 mmol, 1.0 equiv), sodium carbonate (28 mg, 0.26 mmol, 1.0 equiv) and tetrabutylammonium chloride (72 mg, 0.26 mmol, 1.0 equiv) with palladium acetate (6 mg, 0.027 mmol, 0.1 equiv) in DMF (3 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/hexane (1 : 9) afforded pure azabicyclooctane **3.4m** (20 mg, 22%) as a clear oil and a complex mixture of **3.4m'** and **3.4m''** (41 mg, 45%) as a clear oil.

**Analytical data for 3.4m:**  $R_f$  = 0.49 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (d,  $J$  = 2.7 Hz, 0.5H), 7.28 (s, 1H), 7.27 (t,  $J$  = 1.4 Hz, 1H), 7.25 (d,  $J$  = 0.5 Hz, 0.5H), 7.13 (d,  $J$  = 1.9 Hz, 1H), 7.12 (d,  $J$  = 1.9 Hz, 1H), 6.79 (s, 1H), 6.47 (s, 1H), 5.94 (dd,  $J$  = 6.0 Hz,  $J$  = 1.5 Hz, 2H), 4.97 (ddd,  $J$  = 17.2 Hz,  $J$  = 9.9 Hz,  $J$  = 8.4 Hz, 1H), 4.87 (dd,  $J$  = 2.0 Hz, 0.5 Hz, 0.5H), 4.83 (t,  $J$  = 2.1 Hz, 1H), 4.81 (dd,  $J$  = 2.0 Hz,  $J$  = 0.5 Hz, 0.5H), 4.65 (d,  $J$  = 15.0 Hz, 1H), 4.50 (d,  $J$  = 15.0 Hz, 1H), 4.12 (d,  $J$  = 3.3 Hz, 1H), 2.79 (sept,  $J$  = 5.0 Hz, 1H), 2.13 (dd,  $J$  = 12.9 Hz,  $J$  = 9.8 Hz, 1H), 1.64 (s, 3H), 1.17 (dd,  $J$  = 12.9 Hz,  $J$  = 4.7 Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  16.5, 38.9, 44.6, 46.7, 48.5, 62.0, 101.1, 103.6, 105.3, 115.9, 127.6, 128.2 (2C), 128.7 (2C), 131.2, 135.9, 137.1, 140.0, 145.8, 147.2, 174.9; IR ( $\text{cm}^{-1}$ ) 1668, 1622, 1040; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{22}\text{H}_{22}\text{NO}_3$  ( $\text{M}+\text{H}$ ) $^+$  348.1600, found 348.1591.



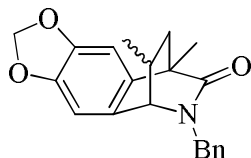
**(5R,7S,8S)-11-benzyl-8-methyl-6-methylene-10-oxo-5,6,7,8-tetrahydro-5,8-**

**(epiminomethano)naphtho[2,3-d][1,3]dioxol-7-yl acetate (3.5).** A solution of azabicyclooctane

**3.4b** and **3.4b'** (207 mg, 0.62 mmol, 1.0 equiv) in acetic acid (3 mL) was injected into a reaction vessel containing the solid reagents including benzoquinone (7 mg, 0.065 mmol, 0.1 equiv) and palladium acetate (7 mg, 0.033 mmol, 0.05 equiv). 30% hydrogen peroxide (78  $\mu$ L, 2.55 mmol, 4.1 equiv) was added by syringe and the resulting mixture was stirred at 75  $^{\circ}$ C for 43.5h, cooled to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (3x30 mL).

The combined organic phase was washed with water (2x40 mL) and brine (2x40 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography over silica eluting with EtOAc/hexane (1:4) to afford azabicyclooctane **3.5** (73 mg, 30%) as yellow heavy oil and recovered starting material **3.4b** and **3.4b'** (38%) with isomer ratio retained:

**Analytical data for 3.5:**  $R_f$  = 0.40 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26-7.27 (m, 3H), 7.13-7.15 (m, 2H), 6.83 (s, 1H), 6.49 (s, 1H), 5.96 (d,  $J$  = 1.4, 1H), 5.93 (d,  $J$  = 1.5, 1H), 5.37 (s, 1H), 5.01 (d,  $J$  = 1.5 Hz, 1H), 4.94 (d,  $J$  = 1.8 Hz, 1H), 4.72 (d,  $J$  = 15.2 Hz, 1H), 4.58 (d,  $J$  = 15.3 Hz, 1H), 4.51 (s, 1H), 2.15 (s, 3H), 1.61 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  12.9, 21.3, 48.6, 51.5, 63.0, 73.9, 101.5, 103.6, 105.4, 112.0, 127.7, 128.3 (2C), 128.6 (2C), 131.4, 133.8, 136.5, 143.9, 147.0, 147.6, 171.2, 171.7; IR ( $\text{cm}^{-1}$ ) 1740, 1672, 700; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{23}\text{H}_{21}\text{NO}_5\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  414.1317, found 414.1319.



**(5*S*,8*R*)-11-benzyl-6,8-dimethyl-5,6,7,8-tetrahydro-5,8-(epiminomethano)naphtho[2,3-d][1,3]dioxol-10-one (3.6).**

**Preparation of azabicyclooctane 3.6 via reduction with Pd on carbon.** A solution of azabicyclooctane **3.4b** and **3.4b'** (193 mg, 0.58 mmol, 1.0 equiv) in MeOH (6 mL) was injected into a reaction vessel containing Pd/C (7.1 mg, 0.067 mmol, 0.1 equiv) in MeOH (14 mL). The flask was flushed with argon, H<sub>2</sub> then stirred overnight at room temperature under H<sub>2</sub> (1 atm). The resulting solution was filtered through celite to afford a diastereomeric mixture of azabicyclooctane **3.6** (156 mg, 80%) as a light yellow oil.

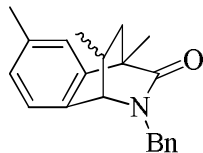
**Preparation of azabicyclooctane 3.6 via reduction with Crabtree's Ir catalyst.** A solution of azabicyclooctane **3.4b** and **3.4b'** (18 mg, 0.055 mmol, 1.0 equiv) in DCM (2 mL) was injected into a reaction vessel containing Crabtree's Ir catalyst (3.9 mg, 0.0048 mmol, 0.09 equiv) in DCM (2 mL). The flask was flushed with argon, H<sub>2</sub> then stirred overnight at room temperature under H<sub>2</sub> (1 atm). The resulting solution was filtered through celite to afford a diastereomeric mixture of azabicyclooctane **3.6** (17 mg, 94%) as a light yellow oil.

**Analytical data for 3.6 obtained via reduction with Pd on carbon.** *R<sub>f</sub>* = 0.50 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.27 (d, *J* = 2.6 Hz, 0.57H), 7.25 (d, *J* = 1.7 Hz, 0.43H), 7.24 (d, *J* = 2.1 Hz, 0.86H), 7.23 (d, *J* = 1.8 Hz, 1.14H), 7.11 (dd, *J* = 7.8 Hz, *J* = 1.6 Hz, 1.14H), 7.06 – 7.03 (m, 0.86H), 6.78 (s, 0.57H), 6.77 (s, 0.43H), 6.51 (s, 0.57H), 6.40 (s, 0.43H), 5.94 (d, *J* = 1.5 Hz, 0.57H), 5.93 (dd, *J* = 1.5 Hz, *J* = 0.6 Hz, 1H), 5.90 (d, *J* = 1.5 Hz, 0.43H), 5.04 (d, *J* = 14.9 Hz, 0.43H), 4.63 (d, *J* = 15.1 Hz, 0.57H), 4.48 (d, *J* = 15.1 Hz, 0.57H), 4.18 (d, *J* = 14.9 Hz, 0.43H), 4.03 (d, *J* = 1.6 Hz, 0.43H), 4.00 (d, *J* = 3.2 Hz, 0.57H), 2.29 – 2.23 (m, 0.57H), 2.10

(dd,  $J = 12.5$  Hz,  $J = 9.7$  Hz, 0.43H), 1.90 – 1.85 (m, 0.43H), 1.71 (dd,  $J = 12.6$  Hz,  $J = 9.8$  Hz, 0.43H), 1.64 (s, 1.29H), 1.61 (s, 1.71H), 1.29 (dd,  $J = 13$  Hz,  $J = 4.5$  Hz, 0.57H), 1.00 (d,  $J = 6.9$  Hz, 1.29H), 0.85 (dd,  $J = 12.5$  Hz,  $J = 4.7$  Hz, 0.57H), 0.57 (d,  $J = 6.9$  Hz, 1.71H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  [16.5], 16.6, [19.7], 20.2, 34.2, [35.1], [39.9], 40.5, [46.7], 46.8, 48.4, [50.2], 62.7, [63.0], [101.05], 101.08, [103.4], 103.6, [104.0], 105.5, 127.5, [127.6], 128.1 (2C), [128.5 (2C)], [128.6 (2C)], 128.7 (2C), 131.4, [134.8], 135.5, [135.7], [136.9], 137.2, 145.7 (2C), [146.7], [147.0], 175.0, [175.2] Values in brackets are for the minor isomer; IR ( $\text{cm}^{-1}$ ) 1666, 1589, 737; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{21}\text{H}_{21}\text{NO}_3\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  358.1419, found 358.1426.

**Analytical data for 3.6 obtained via reduction with Crabtree's Ir catalyst.**  $R_f = 0.50$

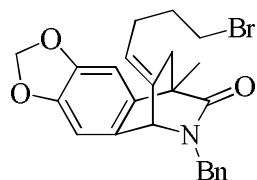
(EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (d,  $J = 2.6$  Hz, 0.40H), 7.25 (d,  $J = 1.7$  Hz, 0.60H), 7.24 (d,  $J = 2.1$  Hz, 1.2H), 7.23 (d,  $J = 1.8$  Hz, 0.8H), 7.11 (dd,  $J = 7.8$  Hz,  $J = 1.6$  Hz, 0.8H), 7.06 – 7.03 (m, 1.2 H), 6.78 (s, 0.4H), 6.77 (s, 0.6H), 6.51 (s, 0.4H), 6.40 (s, 0.6H), 5.94 (d,  $J = 1.5$  Hz, 0.4H), 5.93 (dd,  $J = 1.5$  Hz,  $J = 0.6$  Hz, 1H), 5.90 (d,  $J = 1.5$  Hz, 0.6H), 5.04 (d,  $J = 14.9$  Hz, 0.6H), 4.63 (d,  $J = 15.1$  Hz, 0.4H), 4.48 (d,  $J = 15.1$  Hz, 0.4H), 4.18 (d,  $J = 14.9$  Hz, 0.6H), 4.03 (d,  $J = 1.6$  Hz, 0.6H), 4.00 (d,  $J = 3.2$  Hz, 0.4H), 2.29 – 2.23 (m, 0.4H), 2.10 (dd,  $J = 12.5$  Hz,  $J = 9.7$  Hz, 0.6H), 1.90 – 1.85 (m, 0.6H), 1.71 (dd,  $J = 12.6$  Hz,  $J = 9.8$  Hz, 0.6H), 1.64 (s, 1.8H), 1.61 (s, 1.2H), 1.29 (dd,  $J = 13.0$  Hz,  $J = 4.5$  Hz, 0.4H), 1.00 (d,  $J = 6.9$  Hz, 1.8H), 0.85 (dd,  $J = 12.5$  Hz,  $J = 4.7$  Hz, 0.4H), 0.57 (d,  $J = 6.9$  Hz, 1.2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  16.5, [16.6], 19.7, [20.2], [34.2], 35.1, 39.9, [40.5], 46.7, [46.8], [48.4], 50.2, [62.7], 63.0, 101.05, [101.08], 103.4, [103.6], 104.0, [105.5], [127.5], 127.6, [128.1 (2C)], 128.5 (2C), 128.6 (2C), [128.7 (2C)], [131.4], 134.8, [135.5], 135.7, 136.9, [137.2], [145.7 (2C)], 146.7, 147.0, [175.0], 175.2 Values in brackets are for the minor isomer; IR ( $\text{cm}^{-1}$ ) 1666, 1479, 737; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{21}\text{H}_{21}\text{NO}_3\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  358.1419, found 358.1426.



**(1*S*,4*R*)-10-benzyl-2,4-dimethyl-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one**

**(3.7).** A solution of azabicyclooctane **3.4e** and **3.4e'** (24 mg, 0.080 mmol, 1.0 equiv) in DCM (2 mL) was injected into a reaction vessel containing Crabtree's Ir catalyst (7.0 mg, 0.0087 mmol, 0.11 equiv) in DCM (2 mL). The flask was flushed with argon, H<sub>2</sub> then stirred overnight at room temperature under H<sub>2</sub> (1 atm). The resulting solution was filtered through celite to afford a diastereomeric mixture of azabicyclooctane **3.7** (24 mg, 99%) as a light yellow oil: *R<sub>f</sub>* = 0.51 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.26 (s, 0.34H), 7.25 (t, *J* = 1.9 Hz, 0.68H), 7.22 – 7.21 (m, 2.28H), 7.12 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 0.68H), 7.07 (s, 1H), 7.03 (dd, *J* = 6.5 Hz, *J* = 2.9 Hz, 1.52H), 6.96 (d, *J* = 7.2 Hz, 0.34H), 6.91 (d, *J* = 7.4 Hz, 0.76H), 6.88 (d, *J* = 7.4 Hz, 0.34H), 6.78 (d, *J* = 7.4 Hz, 0.76H), 5.00 (d, *J* = 14.9 Hz, 0.76H), 4.57 (q, *J* = 15.1 Hz, 0.68H), 4.24 (d, *J* = 14.9 Hz, 0.76H), 4.11 (d, *J* = 1.4 Hz, 0.76H), 4.06 (d, *J* = 3.1 Hz, 0.34H), 2.37 (s, 1.02H), 2.35 (s, 2.28H), 2.30-2.24 (m, 0.34H), 2.14 (dd, *J* = 12.5 Hz, *J* = 9.8 Hz, 0.34H), 1.91-1.86 (m, 0.76H), 1.74 (dd, *J* = 12.6 Hz, *J* = 9.9 Hz, 0.76H), 1.66 (s, 2.28H), 1.65 (s, 1.02H), 1.32 (dd, *J* = 12.6 Hz, *J* = 4.5 Hz, 0.76H), 1.00 (d, *J* = 6.9 Hz, 2.28H), 0.88 (dd, *J* = 12.5 Hz, *J* = 4.8 Hz, 0.34H), 0.55 (d, *J* = 6.9 Hz, 0.34H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 16.17, [16.24], 19.8, [20.2], 21.67, [21.72], [34.1], 35.0, 39.9, [40.6], 46.7, [46.8], [48.5], 50.2, [62.5], 62.8, 121.3, [122.4], 122.9, [123.7], [126.5 (2C)], 126.6, 127.5, [128.2 (2C)], 128.5 (2C), 128.57 (2C), [128.60 (2C)], [134.9], 136.9, 137.0, [137.2], [137.4], 138.9, 141.0, [141.9], [175.1], 175.2. Values in brackets are for the minor isomer; IR (cm<sup>-1</sup>) 1664, 1454, 733; HRMS (ES<sup>+</sup>) calcd for C<sub>21</sub>H<sub>24</sub>NO (M+H)<sup>+</sup> 306.1858, found 306.1857.





**(5*S*,8*R*,*E*)-11-benzyl-6-(4-bromobutylidene)-8-methyl-5,6,7,8-tetrahydro-5,8-**

**(epiminomethano)naphtho[2,3-*d*][1,3]dioxol-10-one (3.9)** . A solution of azabicyclooctane

**3.4b** (39 mg, 0.12 mmol, 1.0 equiv) in dichloromethane (5 mL) was injected into a pressure tube

containing the Ru catalyst (Grubbs Catalyst, 2<sup>nd</sup> Generation) (5 mg, 0.0059 mmol, 0.05 equiv),

followed by injecting neat 5-bromo-1-pentene (21  $\mu$ L, 0.18 mmol, 1.5 equiv). The pressure tube

was flushed with argon, sealed and the resulting mixture stirred at 40 °C for 19h. The crude

product was purified by prep-TLC to afford **3.9** (35 mg, 66%) as a clear colorless oil:  $R_f$  = 0.41

(EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.29-7.27 (m, 2H), 7.26-7.25 (m, 1H), 7.11

(dd,  $J$  = 8.0 Hz,  $J$  = 1.9 Hz, 2H), 6.81 (s, 1H), 6.53 (s, 1H), 5.94 (d,  $J$  = 1.5 Hz, 1H), 5.91 (d,  $J$  =

1.5 Hz, 1H), 5.14 (dt,  $J$  = 7.1 Hz,  $J$  = 2.1 Hz, 1H), 4.62 (d,  $J$  = 15.2 Hz, 1H), 4.51 (d,  $J$  = 15.2

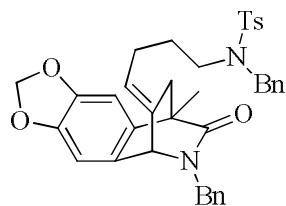
Hz, 1H), 4.45 (s, 1H), 3.25 (dd,  $J$  = 6.6 Hz,  $J$  = 2.3 Hz, 2H), 2.46 (d,  $J$  = 16.1 Hz, 1H), 2.10 (d,  $J$

= 16.1 Hz, 1H), 2.02-1.93 (m, 2H), 1.79 (p,  $J$  = 6.9 Hz, 2H), 1.70 (s, 3H); <sup>13</sup>C NMR (125 MHz,

CDCl<sub>3</sub>)  $\delta$  16.5, 27.1, 32.0, 33.2, 36.7, 47.3, 48.3, 64.7, 101.2, 103.6, 104.1, 121.2, 127.6, 128.2

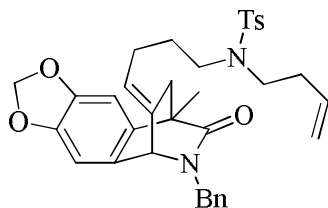
(2C), 128.6 (2C), 133.2, 135.2, 136.5, 136.9, 146.1, 147.1, 174.7; IR (cm<sup>-1</sup>) 1666, 1494, 1037;

HRMS (ES<sup>+</sup>) calcd for C<sub>24</sub>H<sub>24</sub>BrNO<sub>3</sub>Na (M+Na)<sup>+</sup> 476.0837, found 476.0847.



**Preparation of *N*-benzyl-*N*-((*E*)-4-((5*S*,8*R*)-11-benzyl-8-methyl-10-oxo-7,8-dihydro-5,8-epiminomethano)naphtho[2,3-*d*][1,3]dioxol-6(5*H*)-ylidene)butyl)-4-**

**methylbenzenesulfonamide (3.10a).** A solution of alkyl bromide **3.9** (35 mg, 0.077 mmol, 1.0 equiv) in dry DMF (2 mL) was added dropwise at room temperature under nitrogen to a mixture of *N*-benzyl-4-methylbenzenesulfonamide (30 mg, 0.12 mmol, 1.0 equiv) and anhydrous K<sub>2</sub>CO<sub>3</sub> (28 mg, 0.20 mmol, 2.6 equiv) in dry DMF (1 mL). The reaction mixture was stirred at 60 °C for 21.5 h and the crude product purified by preparative TLC to afford **3.10a** (46 mg, 94%) as a clear oil: *R*<sub>f</sub> = 0.41 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.68 (d, *J* = 6.6 Hz, 1H), 7.30 (d, *J* = 6.4 Hz, 2H), 7.29 (s, 1H), 7.28 (s, 2H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 1.0 Hz, 2H), 7.22 (d, *J* = 1.6 Hz, 2H), 7.05 (d, *J* = 2.8 Hz, 1H), 7.03 (d, *J* = 1.4 Hz, 1H), 6.79 (s, 1H), 6.47 (s, 1H), 5.92 (dd, *J* = 12.8 Hz, *J* = 1.2 Hz, 2H), 4.98 (dt, *J* = 5.6 Hz, *J* = 1.6 Hz, 2H), 4.71 (d, *J* = 5.6, 1H), 4.35 (s, 1.5H), 4.31 (s, 0.5H), 4.23 (q, *J* = 9.6 Hz, 2H), 2.97 (t, *J* = 6.0, 2H) 3.44 (s, 3H), 2.24 (d, *J* = 12.8, 1H), 1.90 (d, *J* = 12.8, 1H), 1.67 (s, 3H), 1.64-1.58 (m, 2H), 1.30-1.23 (m, 2H); <sup>13</sup>C NMR δ 16.5, 21.7, 25.8, 27.8, 36.6, 47.3, 48.12, 48.13, 52.5, 64.6, 101.2, 103.6, 104.1, 122.0, 127.3 (2C), 127.5, 128.0, 128.1 (2C), 128.4 (2C), 128.6 (2C), 128.7 (2C), 129.9 (2C), 133.3, 135.3, 135.5, 136.6, 136.8, 136.9, 143.4, 146.1, 147.0, 174.7; IR (cm<sup>-1</sup>) 1664, 1479, 1159; HRMS (ES<sup>+</sup>) calcd for C<sub>38</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub>SNa (M+Na)<sup>+</sup> 657.2399, found 657.2401.

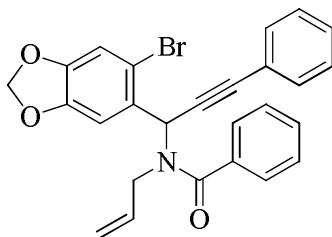


***N*-((*E*)-4-((5*S*,8*R*)-11-benzyl-8-methyl-10-oxo-7,8-dihydro-5,8-epiminomethano)naphtho[2,3-*d*][1,3]dioxol-6(5*H*)-ylidene)butyl)-*N*-(but-3-en-1-yl)-4-**

**methylbenzenesulfonamide (3.10b).** A solution of alkyl bromide **3.9** (37 mg, 0.081 mmol, 1.0 equiv) in dry DMF (2 mL) was added dropwise at room temperature under nitrogen to a mixture of *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (27 mg, 0.12 mmol, 1.5 equiv) and anhydrous K<sub>2</sub>CO<sub>3</sub> (29 mg, 0.21 mmol, 2.6 equiv) in dry DMF (1 mL). The reaction mixture was stirred at 60 °C for 19 h and the crude product purified by preparative TLC to afford **3.10b** (43 mg, 89%) as a cloudy colorless oil: R<sub>f</sub> = 0.40 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.25 (s, 1H), 7.23 (s, 2H), 7.08 (dd, *J* = 7.5 Hz, *J* = 2.0 Hz, 2H), 6.80 (s, 1H), 6.50 (s, 1H), 5.92 (dd, *J* = 18.9 Hz, *J* = 1.3 Hz, 2H), 5.71 – 5.63 (m, 1H), 5.19 (tt, *J* = 7.1 Hz, *J* = 2.0 Hz, 1H), 5.03 (dq, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 5.00 (t, *J* = 1.0 Hz, 1H), 4.74 (d, *J* = 15.2 Hz, 1H), 4.44 (s, 1H), 4.38 (d, *J* = 15.2 Hz, 1H), 3.10 (hept, *J* = 7.5 Hz, 2H), 3.00 (td, *J* = 6.9 Hz, *J* = 1.8 Hz, 2H), 2.41 (s, 3H), 2.38 (d, *J* = 16.9 Hz, 1H), 2.22 (q, *J* = 7.6 Hz, 2H), 2.03 (d, *J* = 16.5 Hz, 1H), 1.81 (hept, *J* = 7.4 Hz, 2H), 1.70 (s, 3H), 1.49 (p, *J* = 7.4 Hz, 2H); <sup>13</sup>C NMR δ 16.5, 21.6, 25.9, 28.3, 33.4, 36.7, 47.3, 47.9, 48.1, 48.2, 64.6, 101.2, 103.6, 104.1, 117.2, 122.0, 127.2 (2C), 127.5, 128.1 (2C), 128.6 (2C), 129.8 (2C), 133.3, 134.7, 135.3., 135.7, 136.88, 136.91, 143.3, 146.1, 147.1, 174.7; IR (cm<sup>-1</sup>) 1663, 1479, 1157; HRMS (ES<sup>+</sup>) calcd for C<sub>35</sub>H<sub>39</sub>N<sub>2</sub>O<sub>5</sub>S (M+H)<sup>+</sup> 599.2580, found 599.2573.

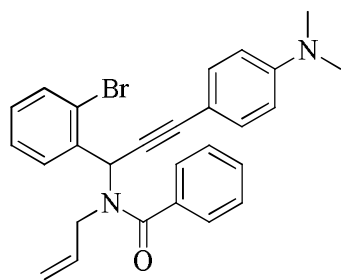
**General protocol for the preparation of amides 4.1a-e and 4.3.** A solution of imine (1.0 equiv.), acid chloride (1.0-1.2 equiv.) and alkyne (1.5-2.0 equiv.) in ACN (6-10 mL) was stirred at room temperature for 5-30 minutes. A separate solution was prepared containing CuCl (20 mol%) in ACN (2-5 mL). The resulting solution and neat DIPEA (1.5 equiv.) were added dropwise simultaneously to the CuCl. The mixture was then allowed to stir at room temperature

for two hours followed by purification via column chromatography to afford enynes **4.1a-e** and **4.3**.



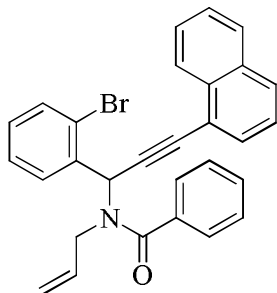
**N-allyl-N-(1-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-phenylprop-2-yn-1-yl)benzamide (4.1b).**

Treatment of (E)-N-((6-bromobenzo[d][1,3]dioxol-5-yl)methylene)-1-phenylmethanamine (467 mg, 1.74 mmol, 1.0 equiv), benzoyl chloride (200  $\mu$ L, 1.72 mmol, 1.0 equiv) and phenylacetylene (382  $\mu$ L, 3.48 mmol, 2.0 equiv) with DIPEA (450  $\mu$ L, 2.29 mmol, 1.5 equiv) and CuCl (34 mg, 0.35 mmol, 0.2 equiv) in ACN (8 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:4) afforded enyne **4.1b** (571 mg, 69%) as a yellow oil:  $R_f$  = 0.30 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 (p,  $J$  = 4.5 Hz, 6H), 7.18 (p,  $J$  = 6.5 Hz, 5H), 6.91 (br s, 1H), 6.69 (br s, 1H), 5.98 (q,  $J$  = 2.5 Hz, 2H), 5.52 (br s, 1H), 5.33 (br s, 1H), 4.64 (d,  $J$  = 15.5 Hz, 1H), 4.39 (d,  $J$  = 14.5 Hz, 1H), 2.02 (br s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  20.8, 47.5, 55.1, 86.4, 87.4, 102.2 (2C), 111.7 (2C), 113.3, 115.5, 117.0, 122.2, 126.8, 127.7 (2C), 128.1, 128.4, 128.7, 128.8, 131.8 (2C), 138.0, 140.4, 147.4, 148.6, 173.0; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 3057, 1643, 1256; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{27}\text{H}_{26}\text{BrN}_2\text{O}$  ( $\text{M}+\text{H}$ ) $^+$  473.1228, found 473.1234.



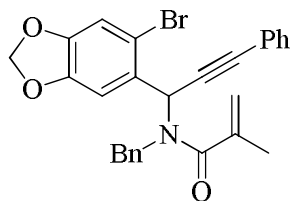
***N*-allyl-*N*-(1-(2-bromophenyl)-3-(4-(dimethylamino)phenyl)prop-2-yn-1-yl)benzamide**

**(4.1d)** Treatment of (E)-*N*-(2-bromobenzylidene)prop-2-en-1-amine (645 mg, 2.88 mmol, 1.0 equiv), benzoyl chloride (335  $\mu$ L, 2.88 mmol, 1.0 equiv) and 4-ethynyl-*N,N*-dimethylaniline (838 mg, 5.77 mmol, 2.0 equiv) with DIPEA (751  $\mu$ L, 4.32 mmol, 1.5 equiv) and CuCl (57 mg, 0.58 mmol, 0.2 equiv) in ACN (8 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:4) afforded enyne **4.1d** (1.102 g, 81%) as a clear red oil:  $R_f$  = 0.48 (EtOAc/hexane 1 : 2.3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.02 (d,  $J$  = 7.0 Hz, 1H), 7.85 (br s, 1H), 7.52 (br s, 2H), 7.42 (d,  $J$  = 8.5 Hz, 4H), 7.36 (t,  $J$  = 7.5 Hz, 2H), 7.21 (t,  $J$  = 6.5 Hz, 1H), 6.68 (d,  $J$  = 8.0 Hz, 2H), 6.02 (br s, 1H), 5.61 (br d,  $J$  = 47.5 Hz, 1H), 4.81 (d,  $J$  = 10.0 Hz, 1H), 4.67 (br s, 1H), 3.98 (br s, 1H), 3.63 (br s, 1H), 3.00 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  40.4, (46.1), 49.2, (50.9), 56.6, 83.8, (87.7), 89.2, 109.0, 111.9, 116.2, 124.7, 127.4 (2C), 127.8, 128.2 (2C), 129.9, 130.2, 132.0 (2C), 132.9 (2C), 133.4, 134.0, 134.6, 135.9, 136.5, 150.5, 171.8; Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 3057, 2218, 1643, 1394; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{27}\text{H}_{26}\text{BrN}_2\text{O}$  ( $\text{M}+\text{H}$ ) $^+$  473.1228, found 473.1220.



***N*-allyl-*N*-(1-(2-bromophenyl)-3-(naphthalen-1-yl)prop-2-yn-1-yl)benzamide (**4.1e**).**

Treatment of (*E*)-*N*-(2-bromobenzylidene)prop-2-en-1-amine (389 mg, 1.74 mmol, 1.0 equiv), benzoyl chloride (200  $\mu$ L, 1.72 mmol, 1.0 equiv) and 1-ethynylnaphthalene (525 mg, 3.45 mmol, 2.0 equiv) with DIPEA (450  $\mu$ L, 2.59 mmol, 1.5 equiv) and CuCl (35 mg, 0.35 mmol, 0.2 equiv) in ACN (8 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:4) afforded enyne **4.1e** (596 mg, 71%) as a clear red oil:  $R_f$  = 0.60 (EtOAc/hexane 1 : 2.3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.38 (d,  $J$  = 8.0 Hz, 1H), 8.11 (d,  $J$  = 7.5 Hz, 1H), 7.90 (d,  $J$  = 8.0 Hz, 2H), 7.79 (d,  $J$  = 7.0 Hz, 1H), 7.61 (t,  $J$  = 7.0 Hz, 2H), 7.56 (t,  $J$  = 7.0 Hz, 2H), 7.50-7.38 (m, 6H), 7.26 (t,  $J$  = 7.5 Hz, 1H), 6.23 (br s, 1H), 5.69 (br s, 1H), 4.87 (d,  $J$  = 10.0 Hz, 1H), 4.81 (br s, 1H), 4.09 (br s, 1H), 3.76 (br s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  (46.3), 49.5, (51.1), 56.7, 60.5, 91.0, 116.8, 120.1, 124.8, 125.3, 126.1, 126.7, 127.2, 127.4, 127.6 (2C), 128.4 (2C), 128.6, 129.4, 130.1, 130.4, 131.0, 131.9, 133.3, 133.5, 133.6, 134.1, 135.6, 136.3, 171.9; Signals for the minor rotamer are given in the parentheses. Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 3059, 2210, 1643, 1396; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{29}\text{H}_{22}\text{BrNONa}$  ( $\text{M}+\text{Na}$ ) $^+$  502.0782, found 502.0792.



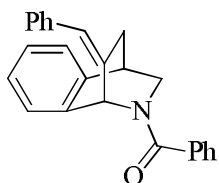
***N*-benzyl-*N*-(1-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-3-phenylprop-2-yn-1-yl)methacrylamide (4.3).**

Treatment of imine **3.1b** (527 mg, 1.66 mmol, 1.0 equiv), methacryloyl chloride (200  $\mu$ L, 2.06 mmol, 1.2 equiv) and phenyl acetylene (250  $\mu$ L, 2.28 mmol, 1.4 equiv) with DIPEA (430  $\mu$ L, 2.47 mmol, 1.5 equiv) and CuCl (38 mg, 0.38 mmol, 0.2 equiv) in ACN (15 mL) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:4) afforded enyne **4.1e** (398 mg, 50%) as a white solid: mp 98-105  $^{\circ}$ C;  $R_f$  = 0.40 (EtOAc/hexane 1 : 2.3);

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 (q,  $J$  = 6.6 Hz, 5H), 7.17 (q,  $J$  = 10.0 Hz, 5H), 6.91 (s, 1H), 6.69 (s, 1H), 5.98 (q,  $J$  = 2.0 Hz, 2H), 5.54 (s, 1H), 5.33 (s, 2H), 4.64 (d,  $J$  = 15.9 Hz, 1H), 4.39 (d,  $J$  = 14.4 Hz, 1H), 2.02 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  20.8, 47.5, 55.1, 86.4, 87.4, 102.2, 111.7, 113.3, 115.5, 117.0, 122.2, 126.8, 127.7 (2C), 128.1 (2C), 128.4 (2C), 128.7, 128.8, 131.8 (2C), 138.0, 140.4, 147.4, 148.6, 173.0; Signals for the minor rotamer are given in the parentheses. Significant signal broadening of some signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR arises due to hindered rotation about the amide bond. See temperature dependent  $^1\text{H}$  NMR spectra for **3.2b**; IR ( $\text{cm}^{-1}$ ) 3053, 1647, 1622, 1477, 1265, 737; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{27}\text{H}_{22}\text{BrNO}_3\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  510.0681, found 510.0691.

**General protocol for the preparation of azabicyclooctanes 4.4a-e and 4.4c-d'.** A solution of amide **4.1a-e** (1.0 equiv) in toluene (16 mM) was injected into a reaction flask charged with

AIBN (0.5 equiv), followed by addition of neat tributylstannane (1.5 equiv). The resulting solution was stirred at 100 °C for three hours then purified by column chromatography to afford bicyclocloctanes **4.4a-e** and **4.4c-d'**.



**((1S,4R,Z)-2-benzylidene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-10-**

**yl)(phenyl)methanone (4.4a).** Treatment of amide **4.1a** (221 mg, 0.51 mmol, 1.0 equiv) with

Bu<sub>3</sub>SnH (298 mg, 1.02 mmol, 2.0 equiv) and AIBN (41.8 mg, 0.25 mmol, 0.5 equiv) in toluene (32 mL) according to the general procedure described above, followed by flash chromatography

over silica eluted with EtOAc/Hexane (1:2) afforded azabicyclocloctane **4.4a** (99 mg, 55%) as a

whit solid: mp 110-115 °C; R<sub>f</sub> = 0.16 (EtOAc/hexane 1 : 2.3); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ

7.52-7.48 (m, 5H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 4.3 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 3H),

7.23 – 7.17 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 6.23 (t, *J* = 2.0 Hz, 1H), 5.16 (s, 1H), 3.83 (dd, *J* =

11.9 Hz, *J* = 2.1 Hz, 1H), 3.61 (t, *J* = 2.0 Hz, 1H), 3.50 (dt, *J* = 11.9 Hz, *J* = 2.5 Hz, 1H), 2.96

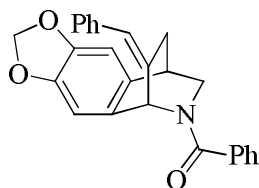
(dt, *J* = 16.8 Hz, *J* = 2.4 Hz, 1H), 2.64 (dq, *J* = 16.8 Hz, *J* = 2.6 Hz, 1H); <sup>13</sup>C NMR (125 MHz,

CDCl<sub>3</sub>) δ 33.0, 35.5, 48.3, 63.0, 122.7, 124.3, 124.8, 127.1 (2C), 127.2, 127.3, 128.3, 128.47

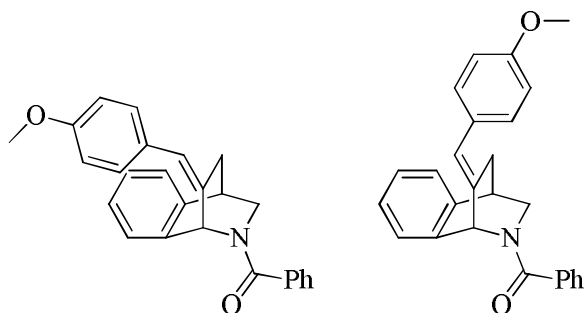
(2C), 128.53 (2C), 128.8 (2C), 129.9, 136.7, 136.8, 137.2, 138.4, 140.9, 170.0; IR (cm<sup>-1</sup>) 1636,

1418, 744; HRMS (ES<sup>+</sup>) calcd for C<sub>25</sub>H<sub>21</sub>NONa (M+Na)<sup>+</sup> 374.1521, found 374.1516.

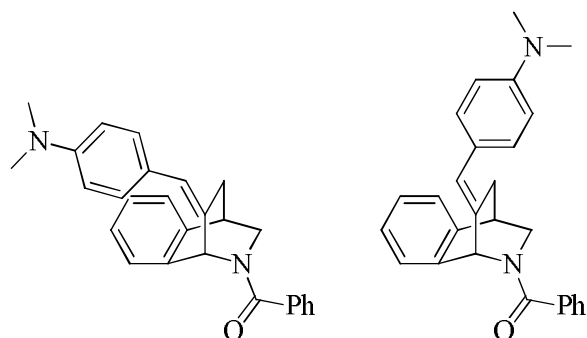




**((5S,8R,Z)-6-benzylidene-5,6,7,8-tetrahydro-5,8-(epiminomethano)naphtho[2,3-d][1,3]dioxol-11-yl)(phenyl)methanone (4.4b).** Treatment of amide **4.1b** (66 mg, 0.14 mmol, 1.0 equiv) with Bu<sub>3</sub>SnH (74  $\mu$ L, 0.28 mmol, 2.0 equiv) and AIBN (12 mg, 0.070 mmol, 0.5 equiv) in toluene (9 mL) according to the general procedure described above, followed by flash chromatography over silica eluted with EtOAc/Hexane (1:2) afforded azabicyclooctane **4.4b** (34 mg, 62%) as a white solid: mp 120-126 °C;  $R_f$  = 0.29 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.23 (dt,  $J$  = 7.5 Hz,  $J$  = 1.0 Hz, 1H), 7.17 (dd,  $J$  = 5.0 Hz,  $J$  = 2.0 Hz, 3H), 7.11 (dd,  $J$  = 8.0 Hz,  $J$  = 1.0 Hz, 2H), 7.04 (t,  $J$  = 7.5 Hz, 2H), 6.94 (dd,  $J$  = 7.0 Hz,  $J$  = 2.0 Hz, 2H), 6.87 (s, 1H), 6.61 (s, 1H), 6.29 (s, 1H), 5.95 (dd,  $J$  = 7.5 Hz,  $J$  = 1.5 Hz, 2H), 5.67 (s, 1H), 3.75 (dd,  $J$  = 12.0 Hz,  $J$  = 2.5 Hz, 1H), 3.467-3.43 (m, 2H), 2.78 (dt,  $J$  = 16.5 Hz,  $J$  = 2.0 Hz, 1H), 2.46 (dq,  $J$  = 16.0 Hz,  $J$  = 3.0 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  33.3, 35.5, 48.9, 55.1, 101.1, 104.3, 106.3, 124.1, 126.9 (2C), 128.2 (4C), 128.5 (2C), 128.8, 129.5, 131.3, 135.2, 135.6, 136.7, 137.4, 146.4, 147.3, 169.8; IR (cm<sup>-1</sup>) 1624, 1479, 1038, 700; HRMS (ES<sup>+</sup>) calcd for C<sub>26</sub>H<sub>22</sub>NO<sub>3</sub> (M+H)<sup>+</sup> 396.1600, found 396.1604.



**((1*S*,4*R*,*E*)-2-(4-methoxybenzylidene)-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-10-yl)(phenyl)methanone (4.4c) and ((1*S*,4*R*,*Z*)-2-(4-methoxybenzylidene)-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-10-yl)(phenyl)methanone (4.4c').** Treatment of amide **4.1c** (105 mg, 0.23 mmol, 1.0 equiv) with Bu<sub>3</sub>SnH (138 mg, 0.47 mmol, 2.0 equiv) and AIBN (19 mg, 0.16 mmol, 0.5 equiv) in toluene (14 mL) according to the general procedure described above, followed by flash chromatography over silica eluted with EtOAc/Hexane (1:2) afforded a diastereomeric mixture of azabicyclooctanes **4.4c** and **4.4c'** (55 mg, 63%) as a cloudy colorless oil: *R*<sub>f</sub> = 0.27 (EtOAc/hexane 1 : 2.3); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.49 (q, *J* = 5.5 Hz, 2.1H), 7.35 (t, *J* = 6.5 Hz, 1.4H), 7.31 (d, *J* = 7.6 Hz, 0.6H), 7.29 (d, *J* = 7.4 Hz, 0.9H), 7.24 (dd, *J* = 3.4 Hz, *J* = 1.3 Hz, 0.6H), 7.20 (d, *J* = 8.8 Hz, 0.6H), 7.16 (dd, *J* = 8.5 Hz, *J* = 1.5 Hz, 1.4H), 7.10 (d, *J* = 7.5 Hz, 1.4H), 7.08 (d, *J* = 1.9 Hz, 0.6H), 6.88 (d, *J* = 8.6 Hz, 1.4H), 6.83 (d, *J* = 8.7 Hz, 0.6H), 6.70 (d, *J* = 8.6 Hz, 1.4H), 6.25 (s, 0.7H), 6.17 (t, *J* = 5.2 Hz, 0.3H), 5.77 (s, 0.7H), 5.13 (s, 0.3H), 3.83 – 3.82 (m, 0.7H), 3.81 (s, 2.1H), 3.80 (d, *J* = 2.2 Hz, 0.3H), 3.79 (s, 0.9H), 3.60 (t, *J* = 2.5 Hz, 0.3H), 3.51 (dt, *J* = 10.8 Hz, *J* = 2.6 Hz, 1.4H), 3.47 (t, *J* = 2.6 Hz, 0.3H), 2.92 (dt, *J* = 16.7 Hz, *J* = 2.3 Hz, 0.3H), 2.80 (dt, *J* = 16.4 Hz, *J* = 2.2 Hz, 0.7H), 2.61 (dq, *J* = 16.5 Hz, *J* = 2.5 Hz, 0.3H), 2.47 (dq, *J* = 16.4, 2.7 Hz, 0.7H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ (33.0), 33.2, 35.4, (35.6), (48.3), 48.8, 55.2, (55.4), 55.5, (63.0), (113.91 (2C)), 113.94 (2C), (122.5), 122.6, 124.29, (124.31), 124.6, 127.0 (2C), (127.1 (2C)), 127.2, (128.1), (128.23 (2C)), 128.24 (2C), (128.4), 128.7, (129.3), 129.42 (2C), (129.43 (2C)), (129.6), 129.7, 129.9, (130.1), (134.8), 135.8, 136.0, (136.7), 138.1, (138.6), (140.9), 141.6, 158.6, (158.7), 169.8, (169.9); IR (cm<sup>-1</sup>) 1626, 1509, 1250, 728; HRMS (ES<sup>+</sup>) calcd for C<sub>26</sub>H<sub>24</sub>NO<sub>2</sub> (M+H)<sup>+</sup> 382.1807, found 382.1800.



**((1*S*,4*R*,*E*)-2-(4-(dimethylamino)benzylidene)-1,2,3,4-tetrahydro-1,4-**

**(epiminomethano)naphthalen-10-yl)(phenyl)methanone (4.4d) and ((1*S*,4*R*,*Z*)-2-(4-**

**(dimethylamino)benzylidene)-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-10-**

**yl)(phenyl)methanone (4.4d').** Treatment of amide **4.1d** (133 mg, 0.28 mmol, 1.0 equiv) with

Bu<sub>3</sub>SnH (150 μL, 0.57 mmol, 2.0 equiv) and AIBN (23 mg, 0.14 mmol, 0.5 equiv) in toluene (18

mL) according to the general procedure described above, followed by flash chromatography over

silica eluted with EtOAc/Hexane (1:2) afforded a diastereomeric mixture of azabicyclooctanes

**4.4d** and **4.4d'** (48 mg, 43%) as a yellow oil: *R*<sub>f</sub> = 0.27 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500

MHz, CDCl<sub>3</sub>) δ 7.49 (s, 1.4H), 7.34 (t, *J* = 7.0 Hz, 1.2H), 7.31 (t, *J* = 7.5 Hz, 1.2H), 7.23 (d, *J* =

8.0 Hz, 0.9H), 7.17 (dd, *J* = 7.5 Hz, *J* = 1.5 Hz, 2.1H), 7.13-7.06 (m, 2.8H), 6.84 (d, *J* = 9.0 Hz,

1.4H), 6.64 (d, *J* = 8.5 Hz, 0.6H), 6.53 (d, *J* = 8.5, 1.4H), 6.24 (s, 0.7H), 6.12 (s, 0.3H), 5.83 (s,

0.7H), 5.11 (s, 0.3H), 3.80 (dd, *J* = 13.5 Hz, *J* = 4.0 Hz, 0.7H), 3.70 (d, *J* = 6.5 Hz, 0.6H), 3.59 (t,

*J* = 2.5 Hz, 0.3H), 5.51 (s, 1.4H), 3.48 (d, *J* = 2.5 Hz, 0.3H), 2.96 (s, 4.2H), 2.94 (s, 1.8H), 2.80

(dt, *J* = 16.5 Hz, *J* = 2.0 Hz, 0.7H), 2.62 (dq, *J* = 17.0 Hz, *J* = 3.0 Hz, 0.3H), 2.64 (dq, *J* = 16.5

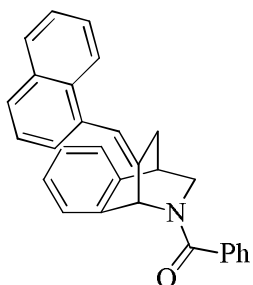
Hz, *J* = 3.0 Hz, 0.7H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ (33.1), 33.2, 35.5, (35.7), (40.5), 40.8,

(48.3), 48.8, 55.3, (63.2), (112.3 (2C)), 112.6 (2C), (122.4), 122.6, (124.3), 124.5, (124.8), 124.9,

125.2, (125.3), (127.0), 127.05 (3C), (127.11 (2C)), (128.0), (128.1 (2C)), 128.2 (2C), (128.7

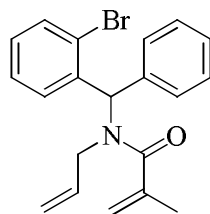
(2C)), 129.1 (2C), 129.3, 129.5, (129.8), (132.5), 134.4, 135.9, (136.8), 138.3, (138.9), (141.0),

141.7, (149.5), 149.6, 169.8, (169.9); IR (cm<sup>-1</sup>) 1628, 1520, 1418, 729; HRMS (ES<sup>+</sup>) calcd for C<sub>27</sub>H<sub>27</sub>N<sub>2</sub>O (M+H)<sup>+</sup> 395.2123, found 395.2116.

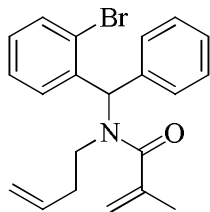


**((1S,4R,Z)-2-(naphthalen-1-ylmethylene)-1,2,3,4-tetrahydro-1,4-**

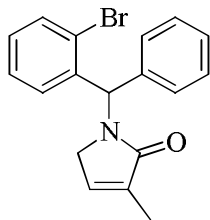
**(epiminomethano)naphthalen-10-yl)(phenyl)methanone (4.4e).** Treatment of amide **4.1b** (58 mg, 0.12 mmol, 1.0 equiv) with Bu<sub>3</sub>SnH (64 μL, 0.24 mmol, 2.0 equiv) and AIBN (10 mg, 0.060 mmol, 0.5 equiv) in toluene (6 mL) according to the general procedure described above, followed by flash chromatography over silica eluted with EtOAc/Hexane (1:2) afforded azabicyclooctane **4.4b** (27 mg, 56%) as a white solid: mp 121-124 °C; R<sub>f</sub> = 0.22 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.94 (dd, *J* = 6.5 Hz, *J* = 2.0 Hz, 1H), 7.89 (dd, *J* = 6.6 Hz, *J* = 2.5 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.53 (m, 2H), 7.39 (d, *J* = 6.9 Hz, 1H), 7.35 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H), 7.2t (td, *J* = 7.4 Hz, *J* = 1.3 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.98 (dt, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 6.95 (d, *J* = 6.8 Hz, 1H), 6.84 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 2H), 6.76 (s, 1H), 6.49 (t, *J* = 7.7 Hz, 2H), 5.53 (s, 1H), 3.86 (dd, *J* = 11.9 Hz, *J* = 2.3 Hz, 1H), 3.58 (p, *J* = 2.4 Hz, 1H), 3.49 (dt, *J* = 11.9 Hz, *J* = 2.6 Hz, 1H), 2.99 (dt, *J* = 16.5 Hz, *J* = 2.2 Hz, 1H), 2.65 (dq, *J* = 16.5 Hz, *J* = 2.8 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 33.0, 35.5, 48.9, 55.9, 122.6, 123.0, 124.6, 125.1, 125.3, 126.2, 126.3, 126.59, 126.61 (2C), 127.3, 127.7 (2C), 128.3, 128.5, 129.2, 132.1, 133.8, 133.9, 135.4, 138.0, 139.0, 141.7, 170.0; IR (cm<sup>-1</sup>) 1628, 1418, 743; HRMS (ES<sup>+</sup>) calcd for C<sub>29</sub>H<sub>24</sub>NO (M+H)<sup>+</sup> 402.1858, found 402.1852.



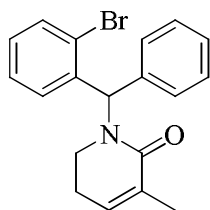
***N*-allyl-*N*-((2-bromophenyl)(phenyl)methyl)methacrylamide (**5.2a**).** Imine **5.1a** (266 mg, 1.19 mmol, 1.0 equiv) and methacryloyl chloride (130  $\mu$ L, 1.34 mmol, 1.1 equiv) were dissolved in DCM (6 mL), after 30 min pyridine (93 mg, 1.18 mmol, 1.0 equiv) was added and the solution was transferred to a vial with NaBPh<sub>4</sub> (407 mg, 1.19 mmol, 1.0 equiv). CuCl (12 mg, 0.12, 0.010 equiv) in DCM (3 mL) was added, and the reaction solution was stirred at room temperature for 24 h. Purification by flash chromatography over silica, eluted with EtOAc/Hexane (1:4) afforded amide **5.2a** (242 mg, 55%) as a clear oil:  $R_f$  = 0.57 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.56 (d,  $J$  = 7.9 Hz, 1H), 7.34 (t,  $J$  = 7.3 Hz, 2H), 7.30 (d,  $J$  = 7.0 Hz, 1H), 7.25 (t,  $J$  = 7.5 Hz, 1H), 7.17 (td,  $J$  = 7.7 Hz,  $J$  = 1.5 Hz, 1H), 7.12 (d,  $J$  = 7.3 Hz, 2H), 7.05 (dd,  $J$  = 7.7 Hz,  $J$  = 1.4 Hz, 1H), 6.80 (br s, 1H), 5.42 (br s, 1H), 5.12 (s, 1H), 4.90 (br s, 1H), 4.72 (d,  $J$  = 10.1 Hz, 1H), 4.59 (d,  $J$  = 16.7 Hz, 1H), 4.15 (d,  $J$  = 12.6 Hz, 1H), 3.90 (dd,  $J$  = 15.2 Hz,  $J$  = 6.1 Hz, 1H), 1.99 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  21.1, 47.9, 65.8, 115.5, 115.8, 116.4, 125.8, 127.5, 127.8, 128.4 (2C), 128.8, 129.6, 131.4, 133.3 (2C), 139.4, 139.6, 140.5, 173.4; Significant signal broadening of some signals in <sup>1</sup>H and <sup>13</sup>C NMR arises due to hindered rotation about the amide bond. See temperature dependent <sup>1</sup>H NMR spectra for **3.2b**; IR (cm<sup>-1</sup>) 1647, 1626, 1437, 700; HRMS (ES<sup>+</sup>) calcd for C<sub>20</sub>H<sub>21</sub>BrNO (M+H)<sup>+</sup> 370.0807, found 370.0807.



***N*-((2-bromophenyl)(phenyl)methyl)-*N*-(but-3-en-1-yl)methacrylamide (**5.2b**).** Imine **5.1b** (552 mg, 2.32 mmol, 1.0 equiv) and methacryloyl chloride (250  $\mu$ L, 2.57 mmol, 1.1 equiv) were dissolved in DCM (6 mL), after 30 min pyridine (190  $\mu$ L, 2.36 mmol, 1.0 equiv) was added and the solution was transferred to a vial with NaBPh<sub>4</sub> (796 mg, 2.33 mmol, 1.0 equiv). CuCl (23 mg, 0.23, 0.010 equiv) in DCM (3 mL) was added, and the reaction solution was stirred at room temperature for 24 h. Purification by flash chromatography over silica, eluted with EtOAc/Hexane (1:4) afforded amide **5.2b** (473 mg, 53%) as a clear oil:  $R_f$  = 0.51 (EtOAc/hexane 1 : 1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.60 (d,  $J$  = 7.9 Hz, 1H), 7.36-7.26 (m, 5H), 7.19 (t,  $J$  = 7.6 Hz, 1H), 7.13 (d,  $J$  = 7.3 Hz, 2H), 7.08 (dd,  $J$  = 7.5 Hz,  $J$  = 1.0 Hz, 1H), 6.72 (s, 1H), 5.41 (s, 1H), 5.10 (s, 1H), 4.80 (d,  $J$  = 9.8 Hz, 1H), 4.65 (dd,  $J$  = 17.0 Hz,  $J$  = 1.5 Hz, 1H), 3.52 (s, 1H), 3.38 (td,  $J$  = 11.0 Hz,  $J$  = 5.0 Hz, 1H), 1.98 (s, 3H), 1.90-1.83 (m, 1H), 1.54-1.46 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  21.1, 32.2, 45.0, 65.7, 115.3, 116.4, 125.3, 127.6, 127.8, 128.4, 128.8 (2C), 129.6, 131.0, 133.4 (2C), 135.1, 139.3, 139.7, 140.5, 173.2; Significant signal broadening of some signals in <sup>1</sup>H and <sup>13</sup>C NMR arises due to hindered rotation about the amide bond. See temperature dependent <sup>1</sup>H NMR spectra for **3.2b**; IR (cm<sup>-1</sup>) 1647, 1624, 1414, 700; HRMS (ES<sup>+</sup>) calcd for C<sub>21</sub>H<sub>23</sub>BrNO (M+H)<sup>+</sup> 384.0963, found 384.0956.

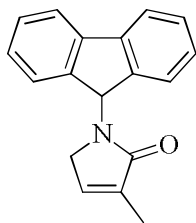


**1-((2-bromophenyl)(phenyl)methyl)-3-methyl-1H-pyrrol-2(5H)-one (5.3a).** A solution of amide **5.2a** (164 mg, 0.44 mmol, 1.0 equiv) in toluene (15 mL) was added to a reaction vessel containing Grubbs I catalyst (35 mg, 0.042 mmol, 0.1 equiv) and the reaction solution was stirred at 45 °C for 2 h. Purification by flash chromatography over silica, eluted with EtOAc/Hexane (1:4) afforded lactam **5.3a** (133 mg, 88%) as a red oil:  $R_f$  = 0.57 (EtOAc/hexane 1 : 2.3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (dd,  $J$  = 8.0 Hz,  $J$  = 1.5 Hz, 1H), 7.34 (t,  $J$  = 1.5 Hz, 0.5 H), 7.32 (s, 1H), 7.31 (s, 0.5H), 7.29 (t,  $J$  = 2.0 Hz, 0.5H), 7.28 (s, 0.5H), 7.25 (d,  $J$  = 1.0 Hz, 0.5H), 7.23 (d,  $J$  = 1.0 Hz, 0.5H), 7.16 (dt,  $J$  = 8.0 Hz,  $J$  = 1.5 Hz, 1H), 7.06 (s, 1H), 7.05 (s, 1H), 6.98 (dd,  $J$  = 7.5 Hz,  $J$  = 1.5 Hz, 1H), 6.78 (s, 1H), 6.69 (q,  $J$  = 2.0 Hz, 1H), 3.67 (dt,  $J$  = 20.0 Hz,  $J$  = 2.0 Hz, 1H), 3.52 (dt,  $J$  = 20.0 Hz,  $J$  = 2.0 Hz, 1H), 1.95 (q,  $J$  = 1.5 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  11.5, 49.7, 59.4, 125.1, 127.4, 127.6, 128.0 (2C), 128.7 (2C), 129.4, 130.1, 133.5, 135.7, 136.0, 139.2, 139.6, 171.8; IR ( $\text{cm}^{-1}$ ) 1681, 1649, 1236, 700; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{18}\text{H}_{16}\text{BrNONa}$  ( $\text{M}+\text{Na}$ ) $^+$  364.0313, found 364.0328.



**1-((2-bromophenyl)(phenyl)methyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (5.3b).** A solution of amide **5.2b** (333 mg, 0.87 mmol, 1.0 equiv) in toluene (20 mL) was added to a reaction vessel containing Grubbs I catalyst (72 mg, 0.087 mmol, 0.1 equiv) and the reaction

solution was stirred at 45 °C for 2 h. Purification by flash chromatography over silica, eluted with EtOAc/Hexane (1:4) afforded lactam **5.3b** (247 mg, 80%) as a pail yellow oil:  $R_f$  = 0.34 (EtOAc/hexane 1 : 1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (dd,  $J$  = 7.9 Hz,  $J$  = 1.2 Hz, 1H), 7.33 (t,  $J$  = 7.3 Hz, 2H), 7.29 (d,  $J$  = 7.3 Hz, 1H), 7.24 (dd,  $J$  = 7.5 Hz,  $J$  = 1.0 Hz, 1H), 7.17 (d,  $J$  = 7.8 Hz, 3H), 7.12 (s, 1H), 7.06 (dd,  $J$  = 7.7 Hz,  $J$  = 1.3 Hz, 1H), 6.35 – 6.29 (q,  $J$  = 1.5 Hz, 1H), 3.19 – 3.02 (m, 2H), 2.34-2.29 (m, 2H), 1.93 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  17.5, 24.3, 43.4, 61.4, 125.3, 127.3, 127.5, 128.4 (2C), 128.7 (2C), 129.2, 130.6, 132.3, 133.59, 133.61, 138.9, 139.4, 165.7; IR ( $\text{cm}^{-1}$ ) 1668, 1628, 1205, 700; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{19}\text{H}_{19}\text{BrNO}$  ( $\text{M}+\text{H}$ ) $^+$  356.0650, found 356.0646.



**1-(9H-fluoren-9-yl)-3-methyl-1H-pyrrol-2(5H)-one (5.4).** A pressure tube charged with lactam **5.3a** (342 mg, 0.15 mmol, 1.0 equiv), palladium acetate (3 mg, 0.015 mmol, 0.1 equiv), cesium carbonate (95 mg, 0.29 mmol, 2.0 equiv) and tetrabutylammonium chloride (38 mg, 0.14 mmol, 1.0 equiv) in DMF (2 mL) was flushed and stirred at 140 °C for 5h. Purification by flash chromatography over silica, eluted with EtOAc/Hexane (1:5) afforded lactam **5.4** (37 mg, 88%) as a red oil:  $R_f$  = 0.4 (EtOAc/hexane 1 : 2.3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (dt,  $J$  = 7.3 Hz,  $J$  = 1.1 Hz, 2H), 7.42 (s, 1.5H), 7.41 (t,  $J$  = 0.8 Hz, 2H), 7.39 (t,  $J$  = 1.0 Hz, 1H), 7.30 (d,  $J$  = 1.1 Hz, 0.5H), 7.29 (d,  $J$  = 0.9 Hz, 1H), 7.27 (d,  $J$  = 1.1 Hz, 0.5H), 6.59 (q,  $J$  = 1.6 Hz, 1H), 6.47 (s, 1H), 3.27 (p,  $J$  = 1.9 Hz, 2H), 2.02 (q,  $J$  = 2.0 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  11.7, 46.6, 57.0, 120.3 (2C), 125.2 (2C), 127.8 (2C), 128.8 (2C), 135.4, 136.1, 140.9, 143.2, 173.2; IR



(cm<sup>-1</sup>) 3065, 1684, 1452, 739; HRMS (ES<sup>+</sup>) calcd for C<sub>18</sub>H<sub>16</sub>NO (M+H)<sup>+</sup> 262.1232, found 262.1238.

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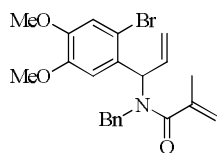
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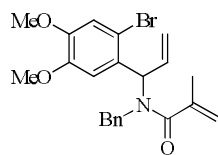
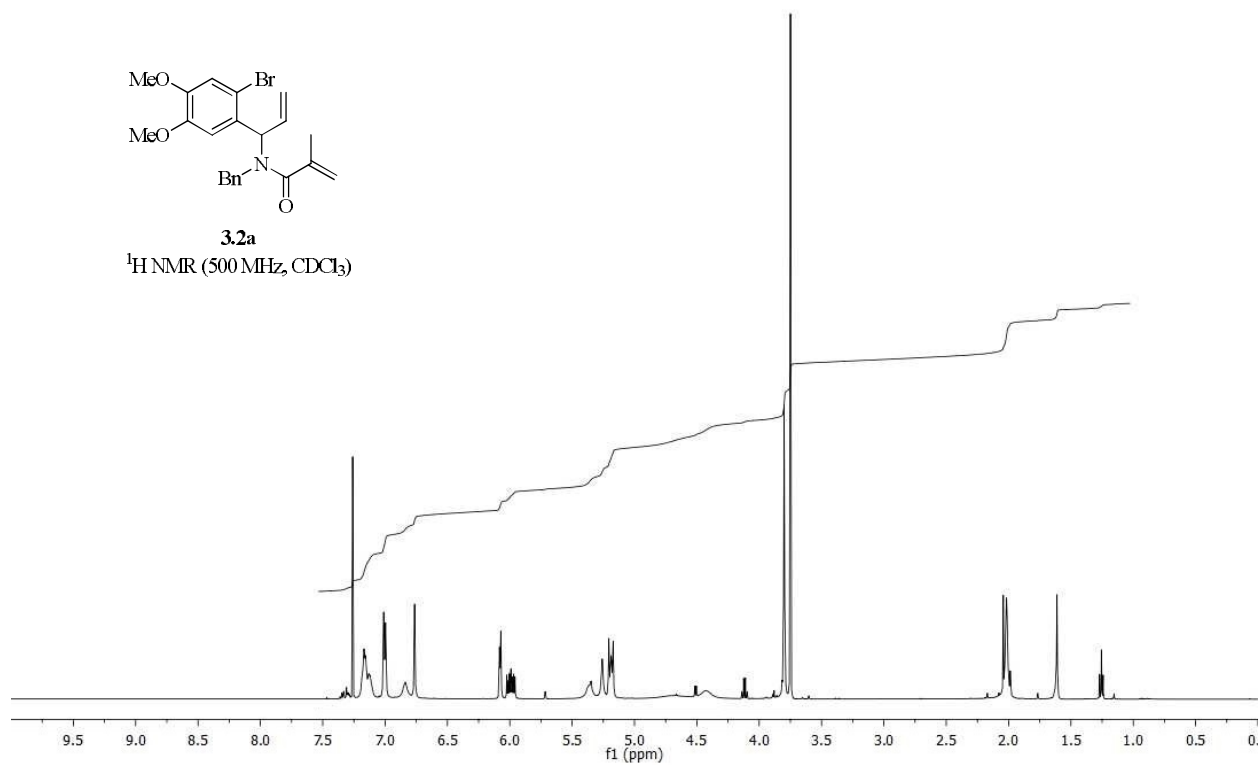
## **Appendix**

*Selected NMR Spectra, GC-MS Spectra and X-Ray Crystallographic Data*



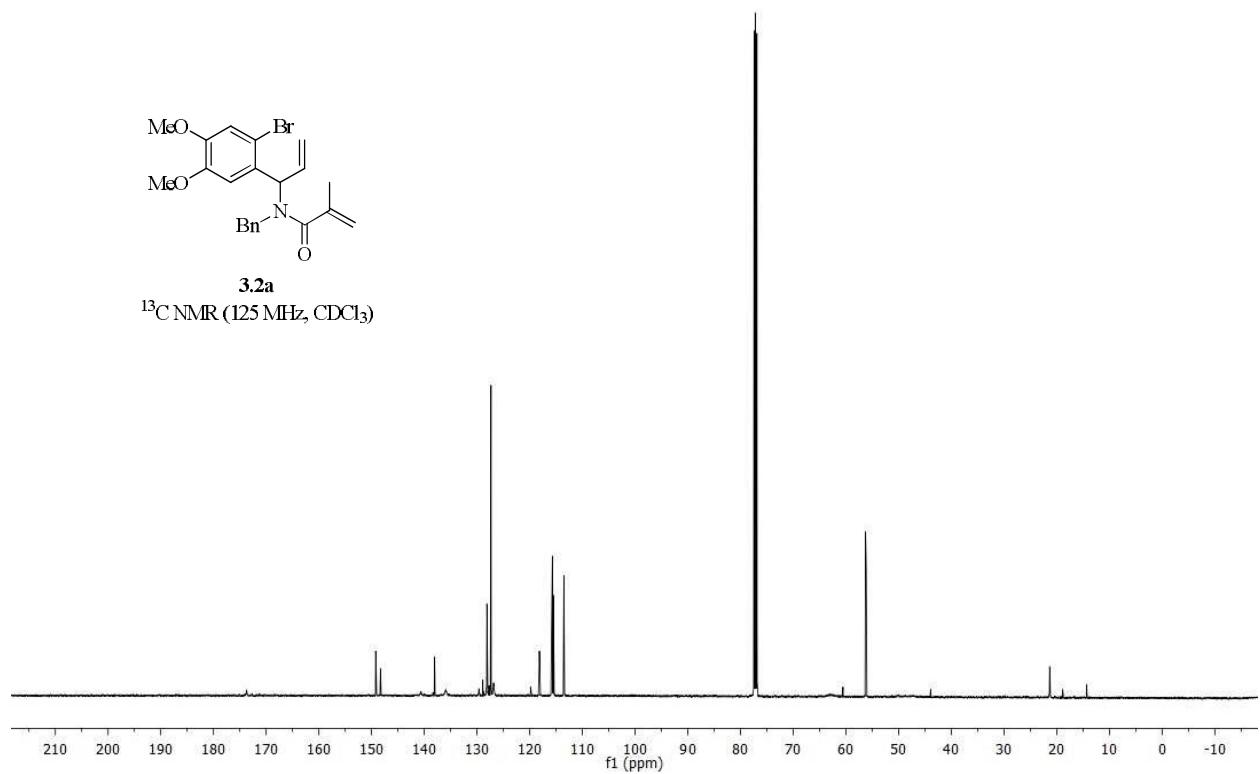
**3.2a**

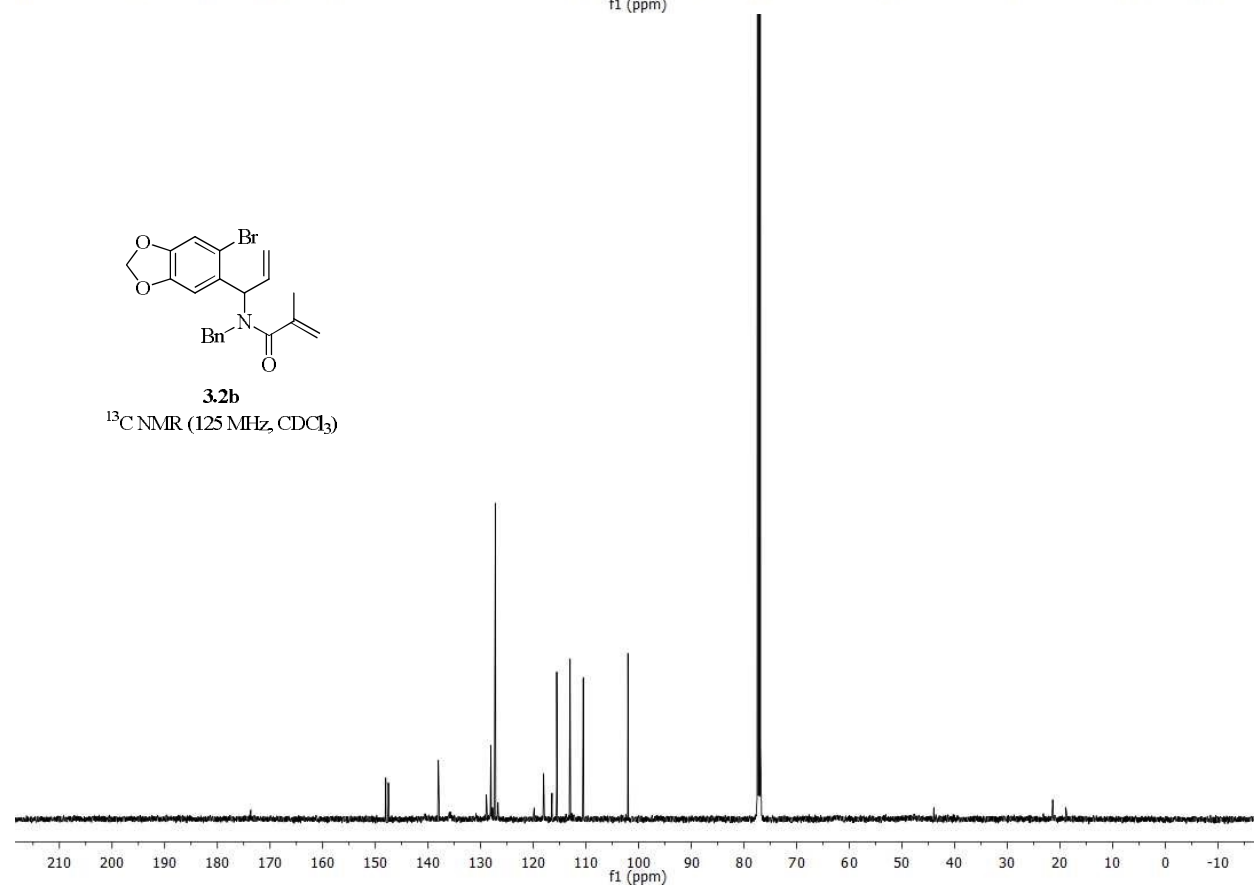
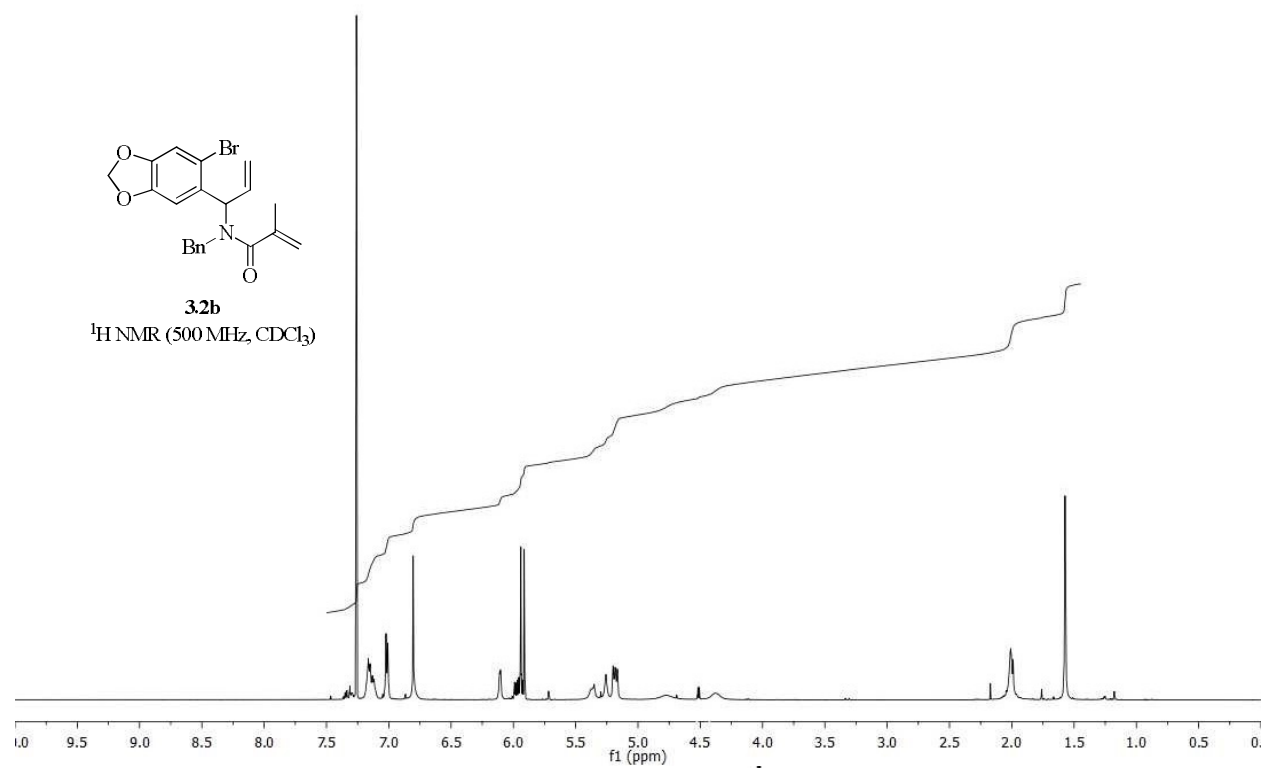
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

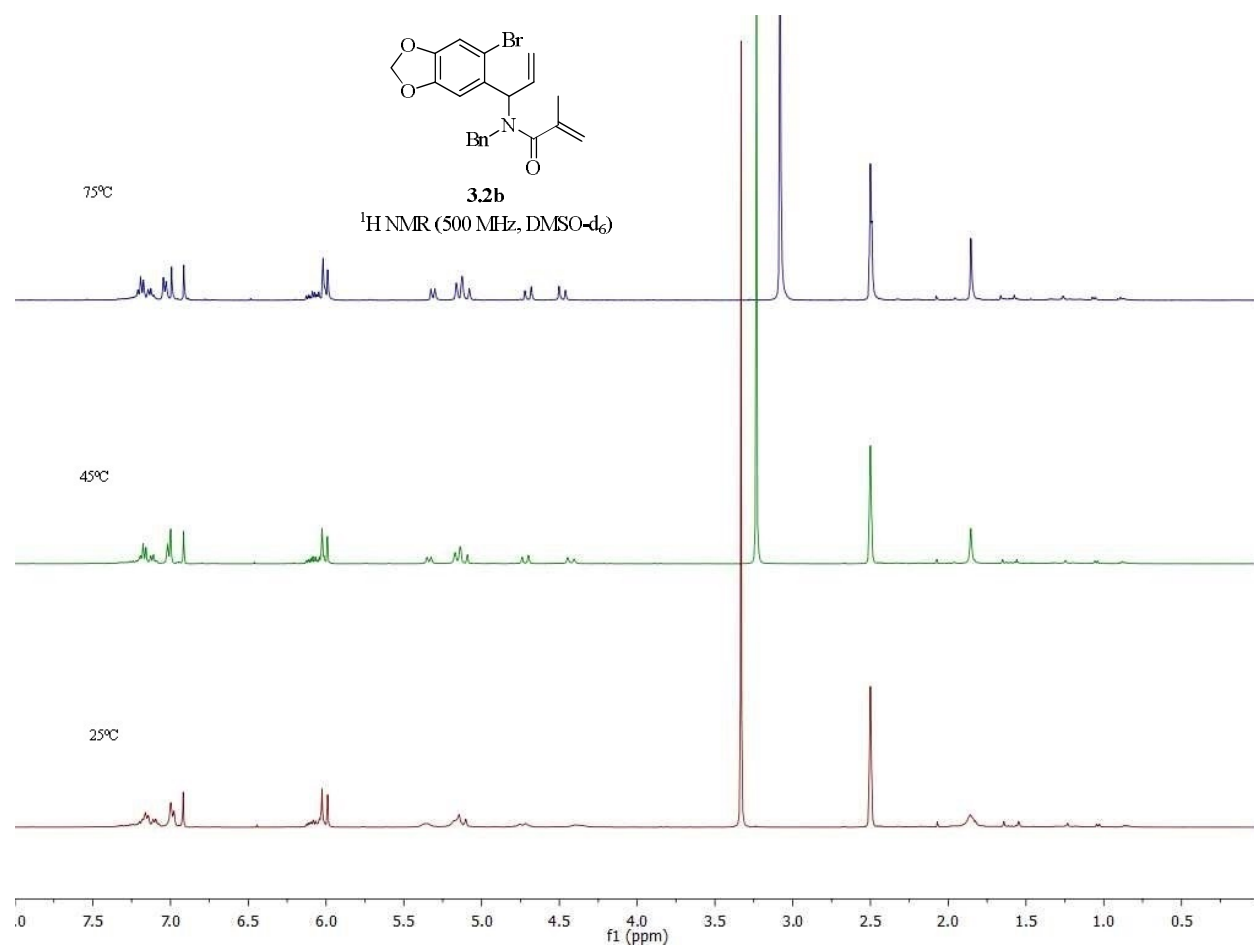


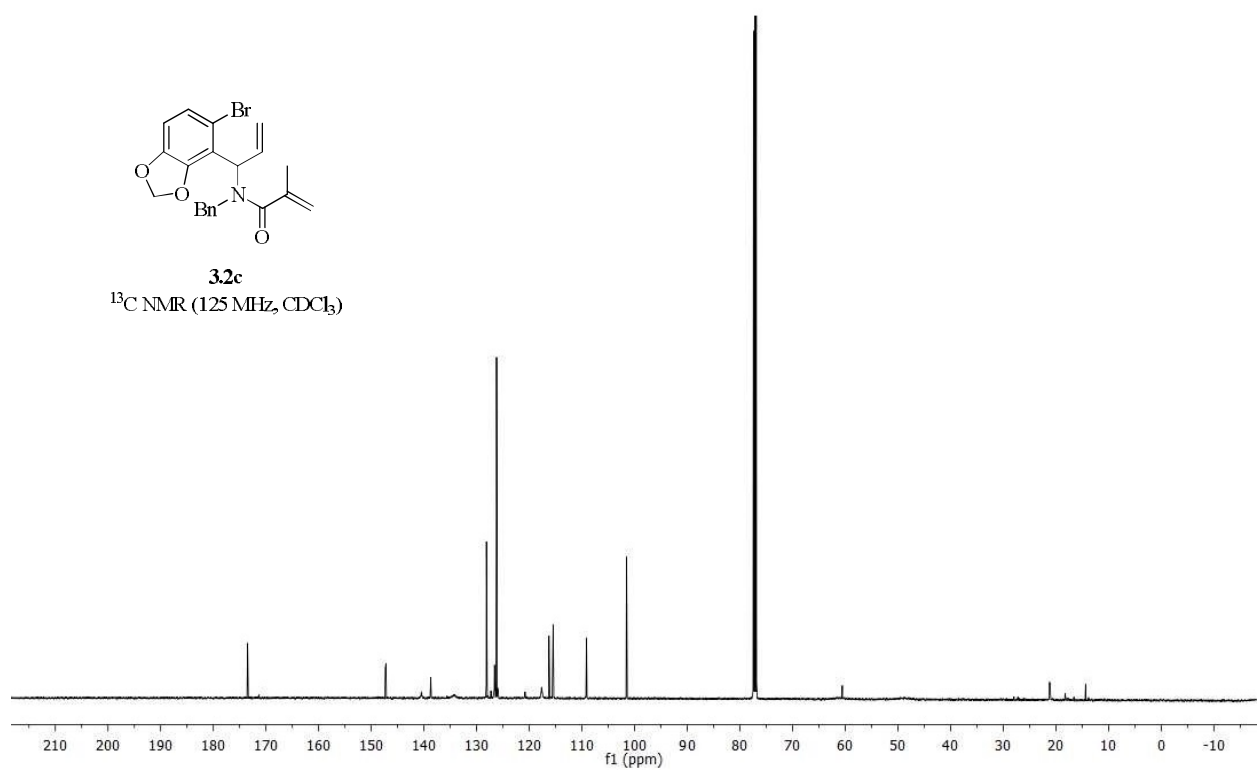
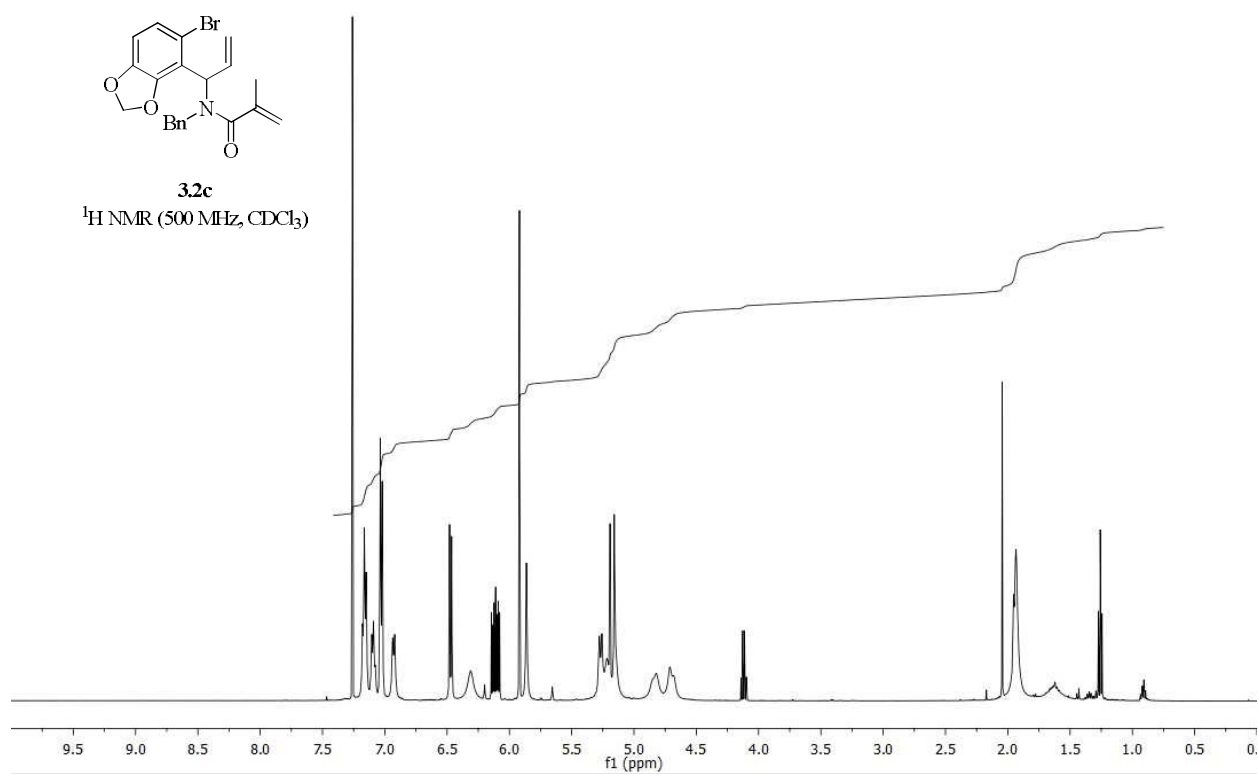
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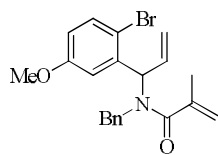






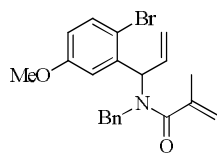
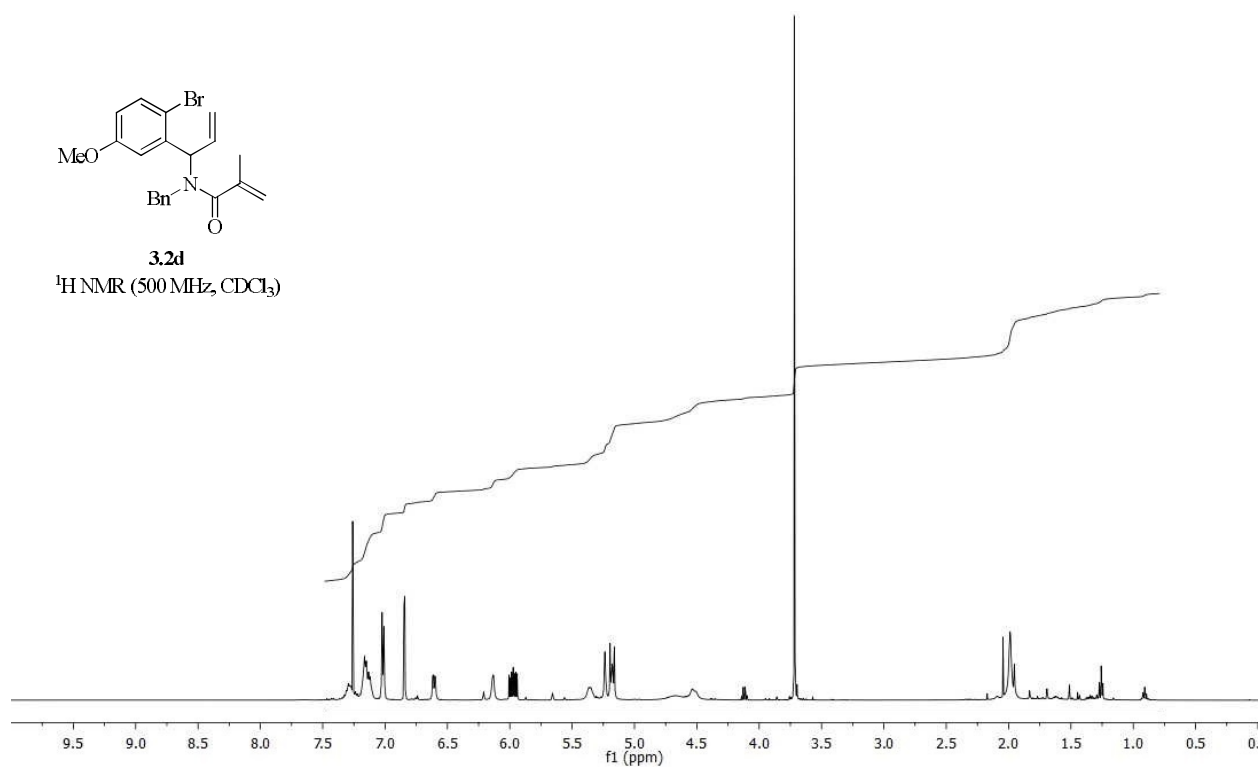






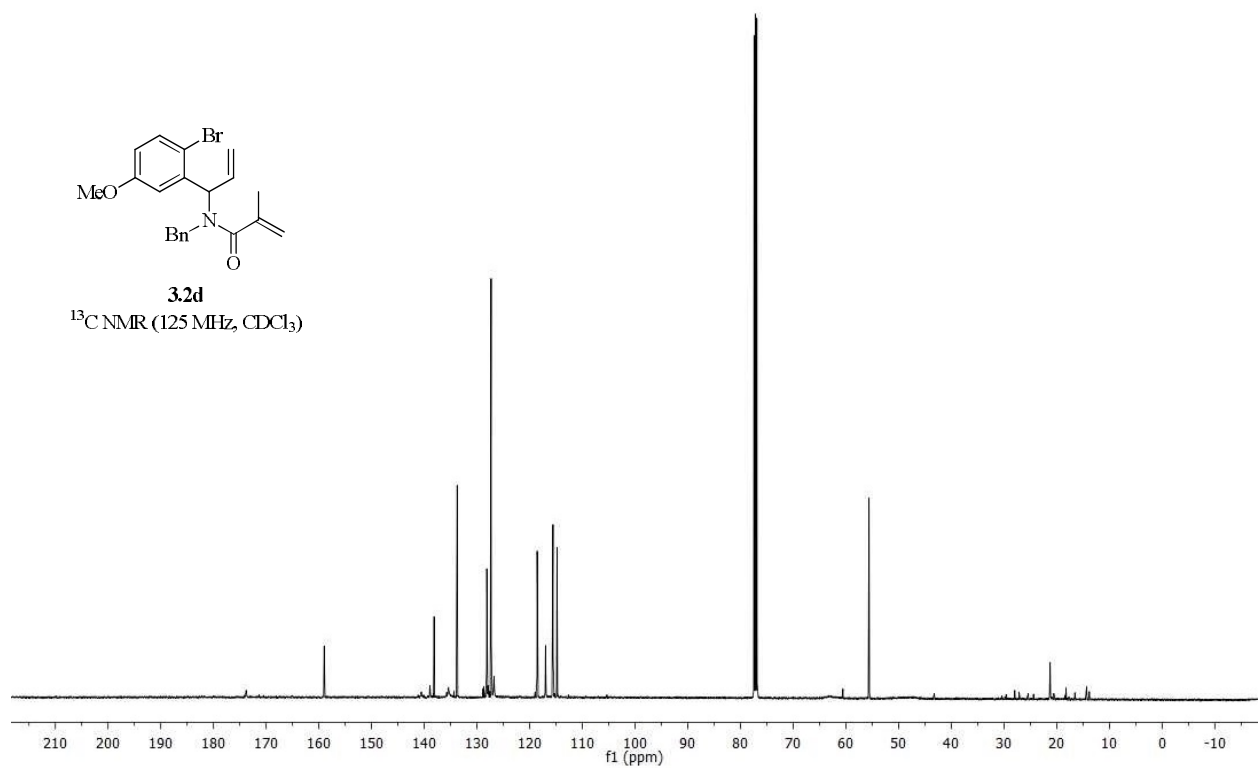
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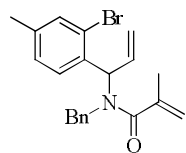
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



**3.2d**

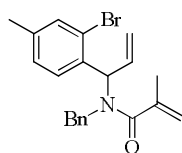
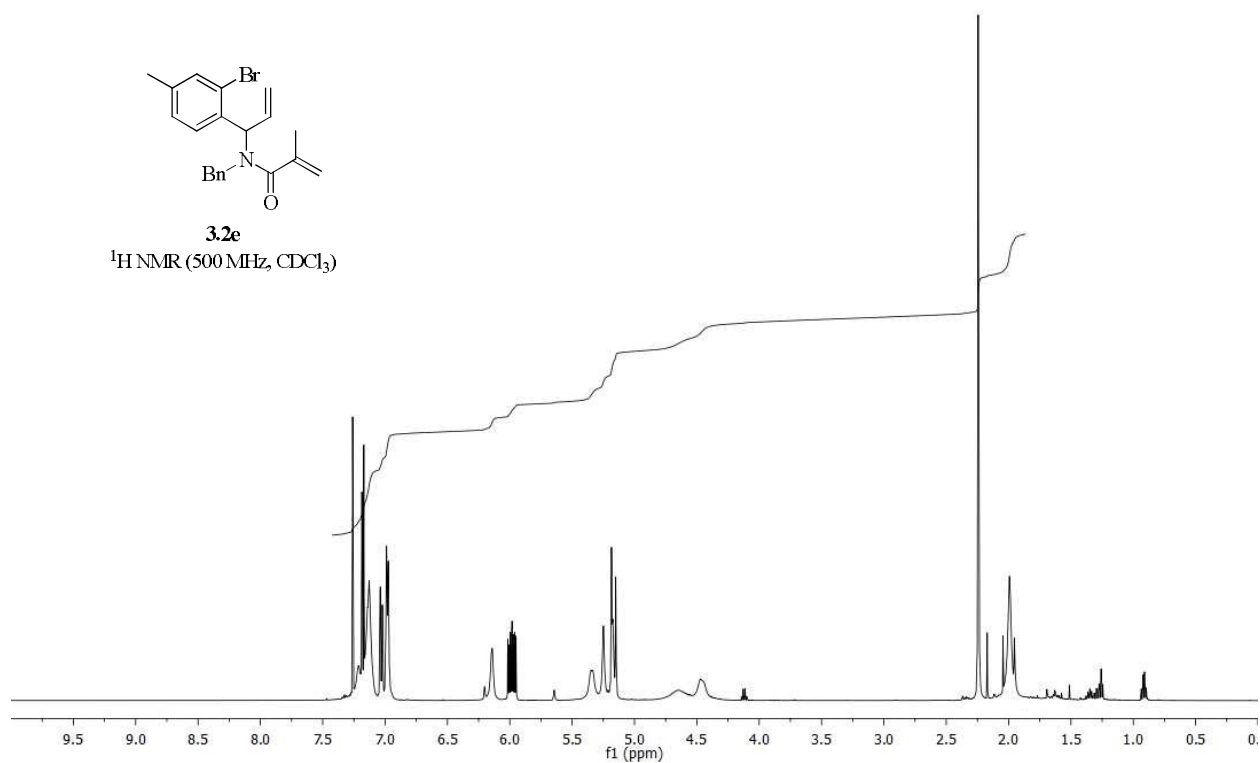
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)





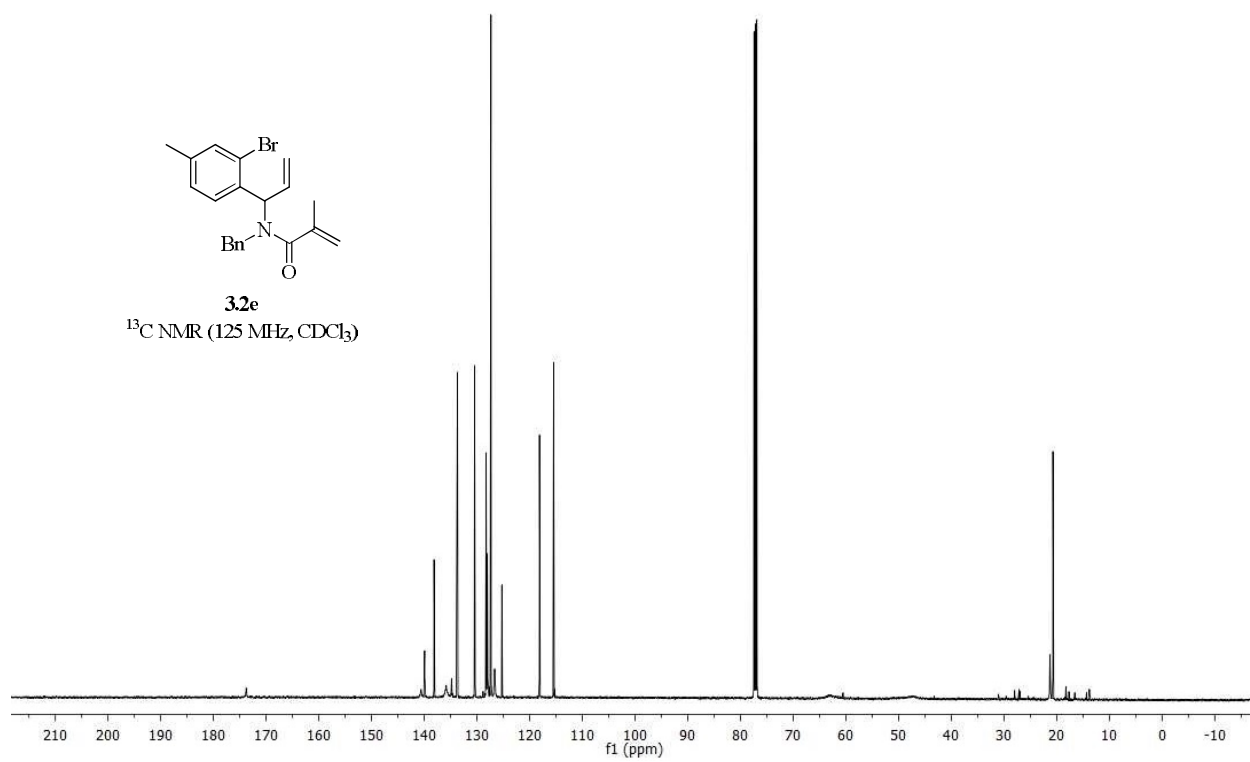
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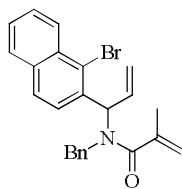
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**3.2e**

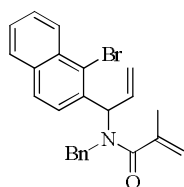
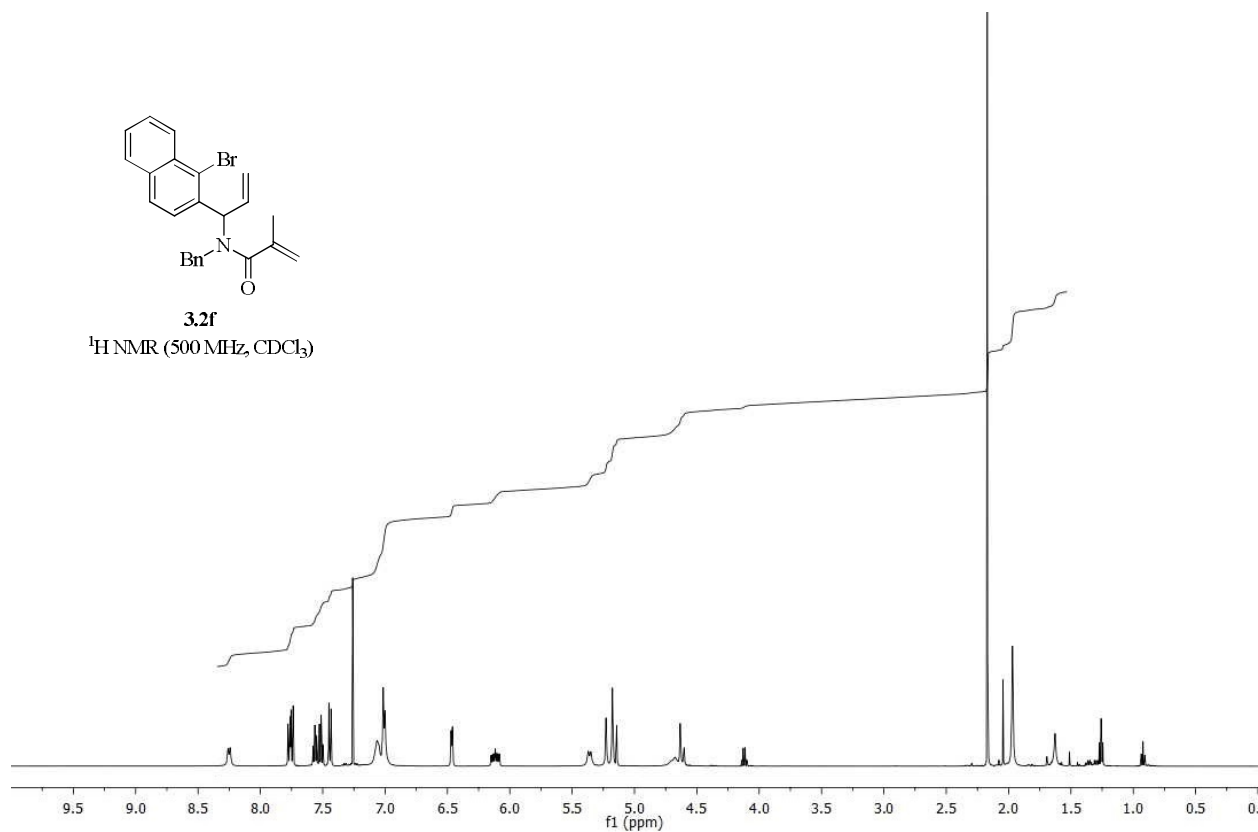
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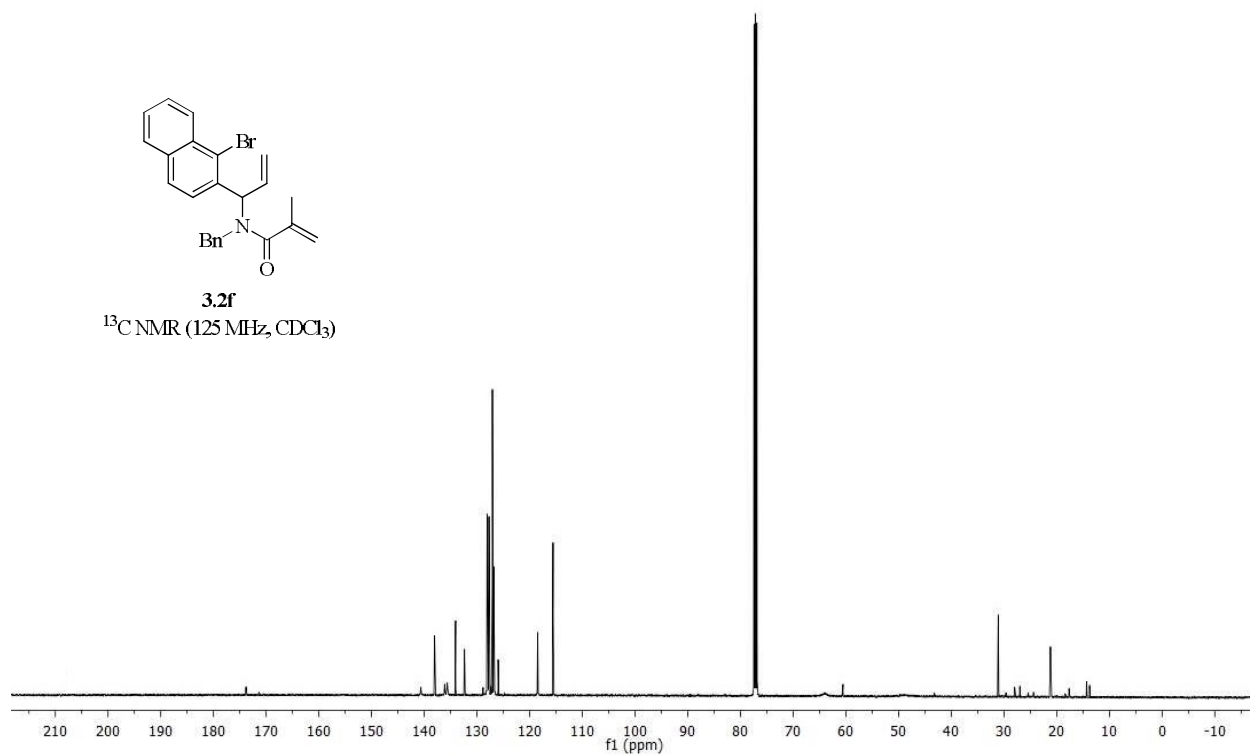
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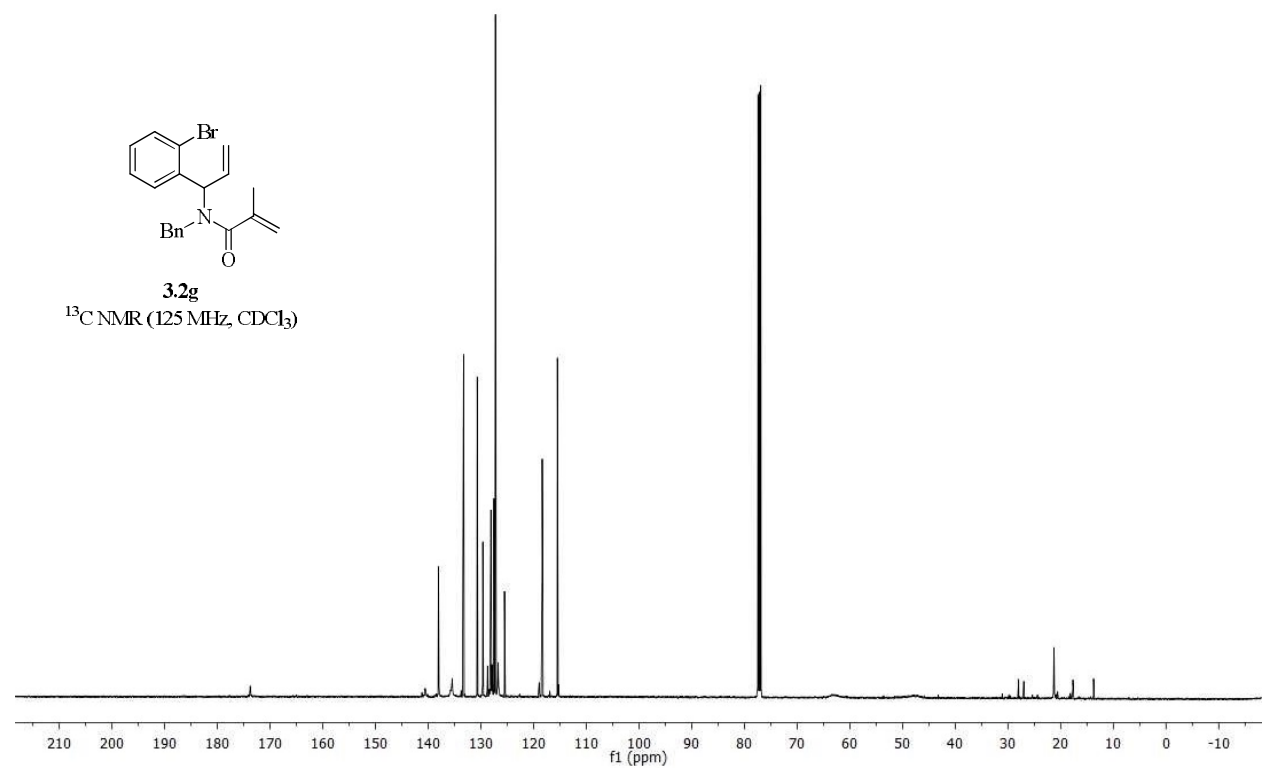
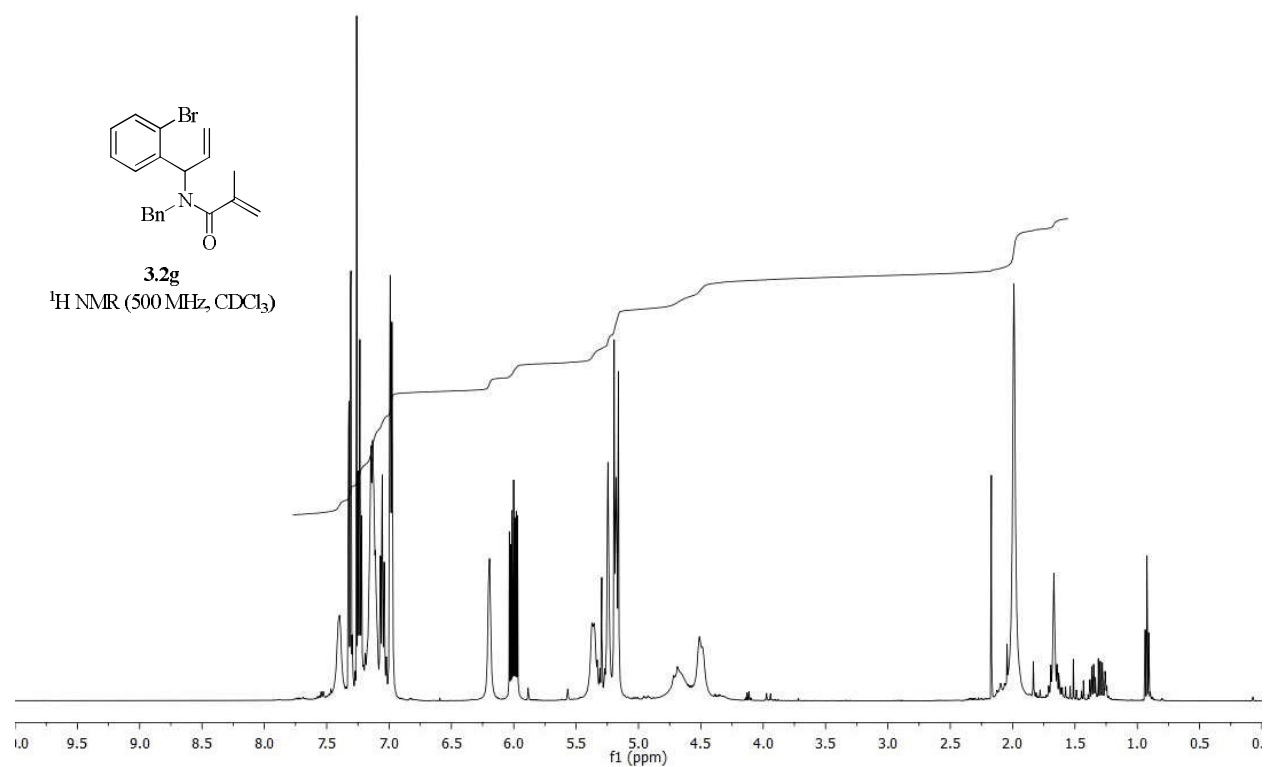
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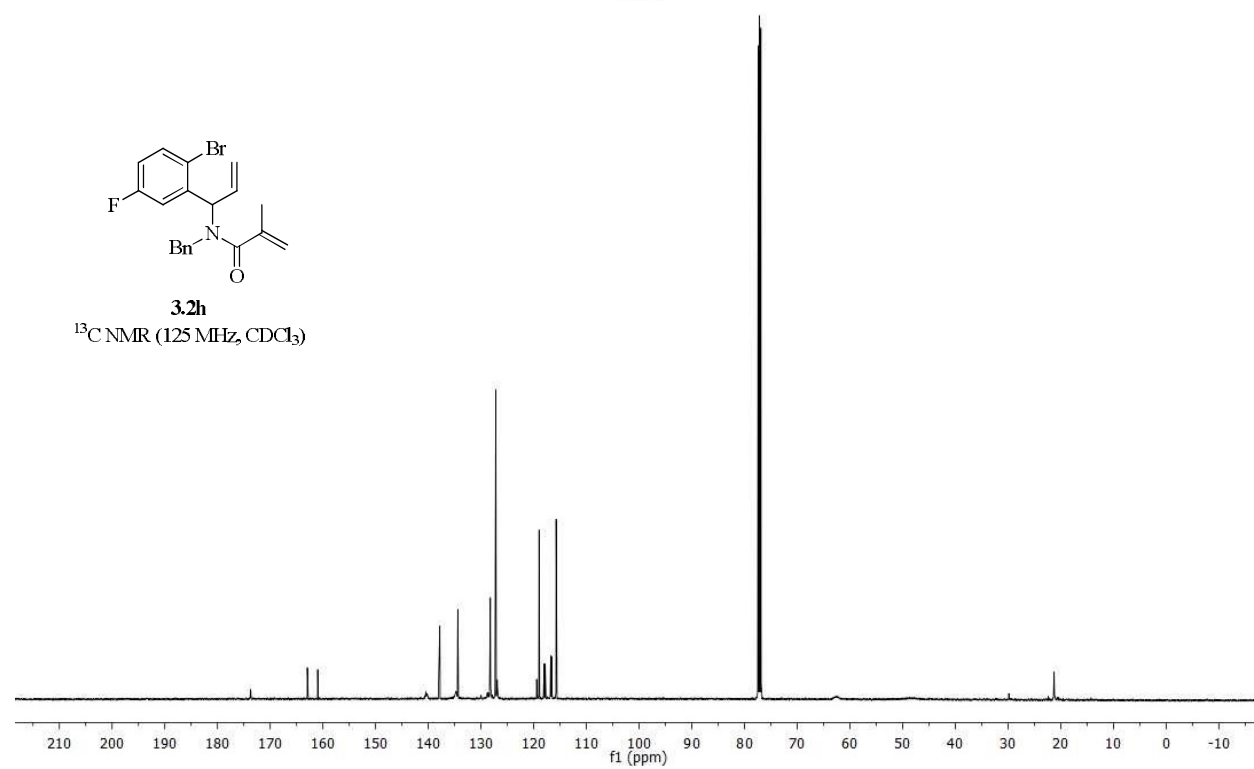
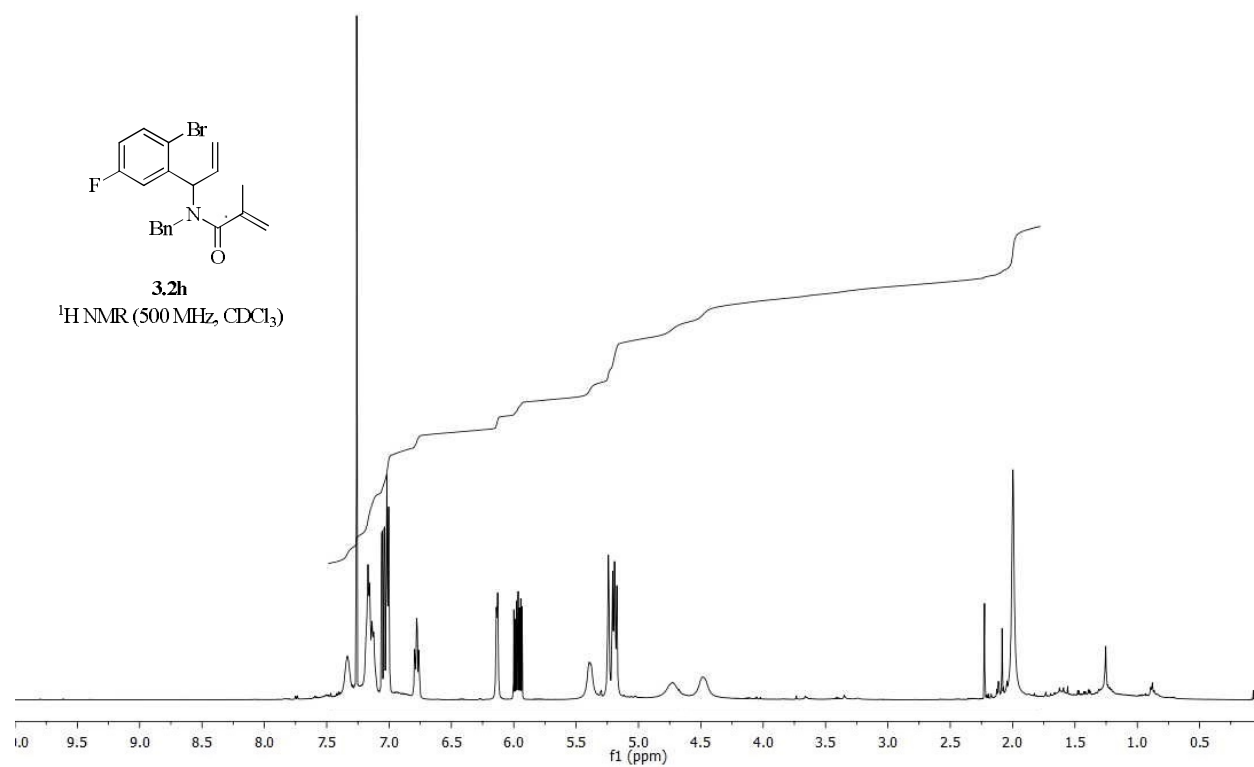


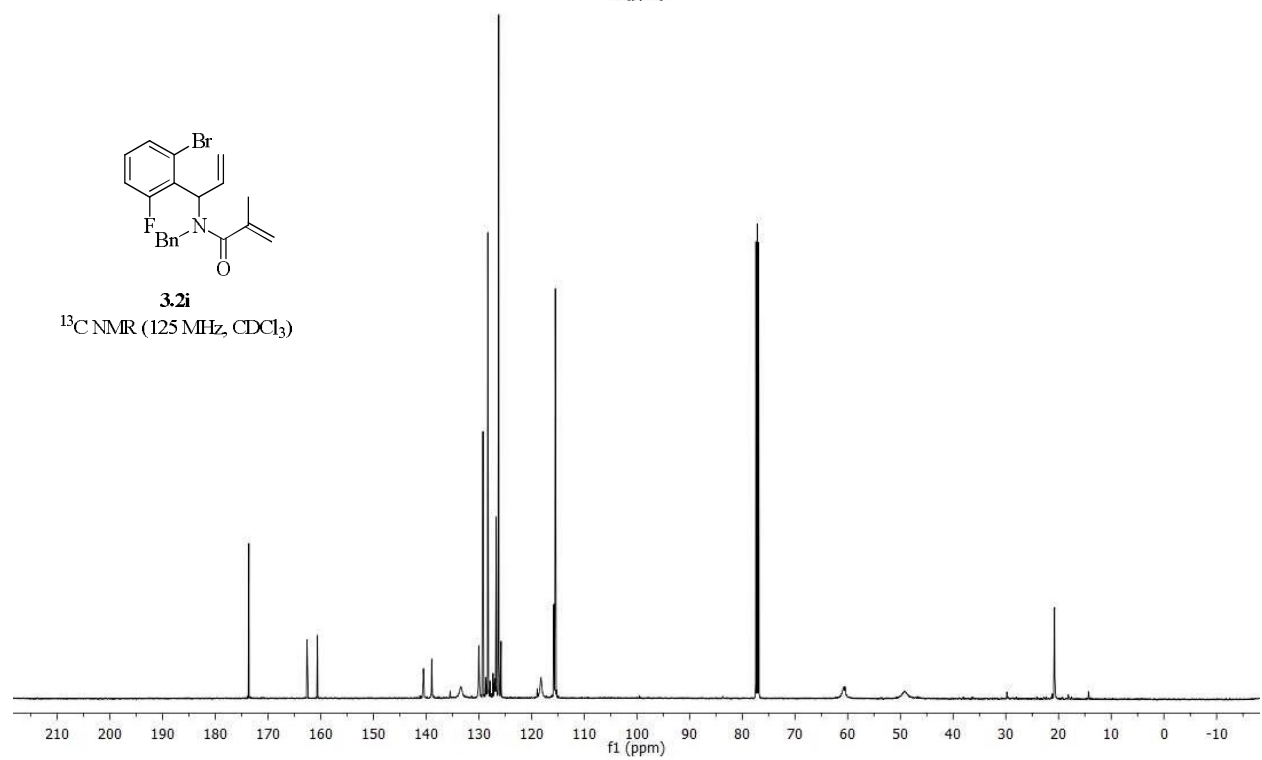
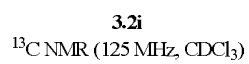
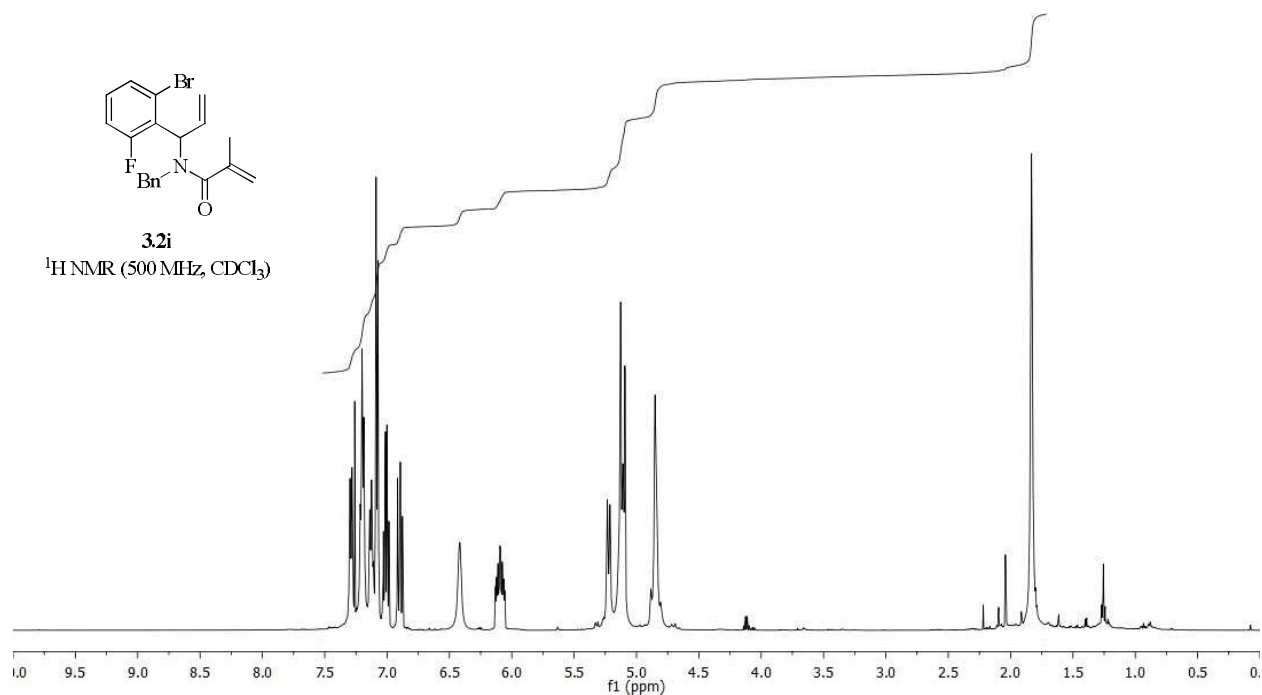
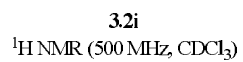
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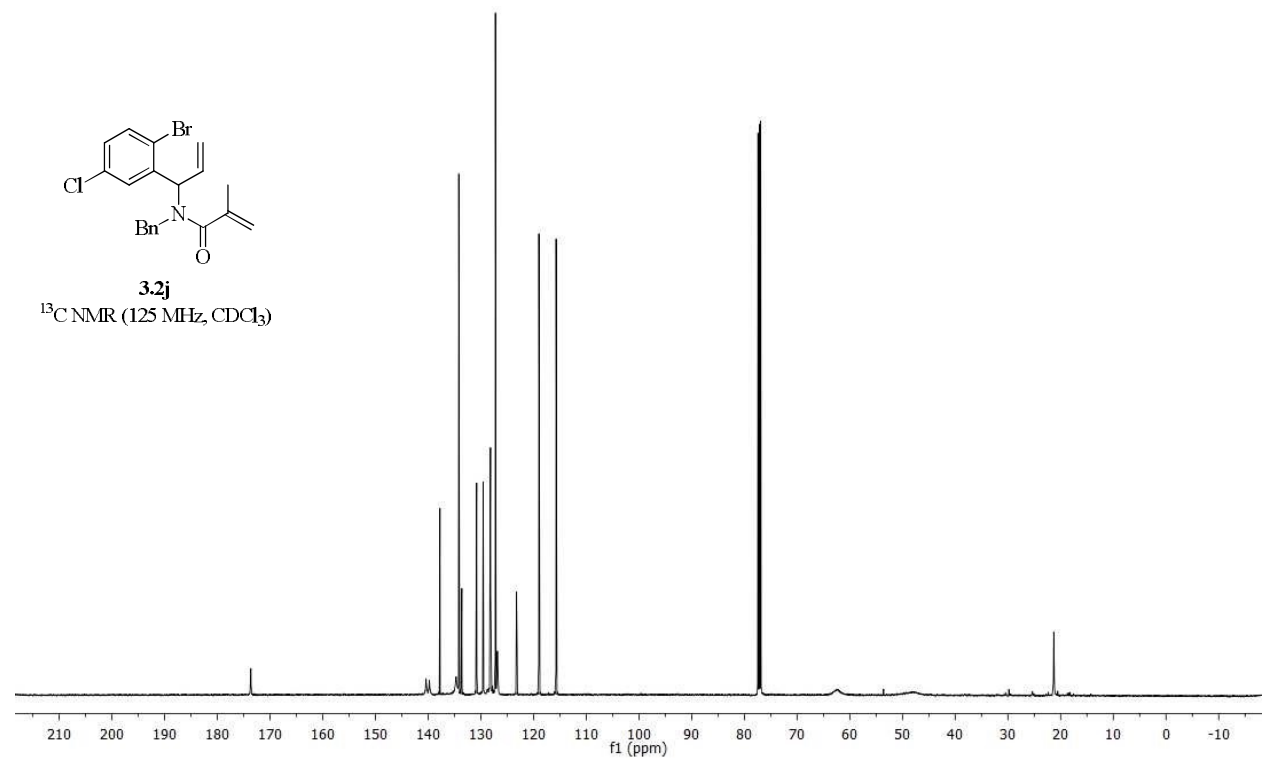
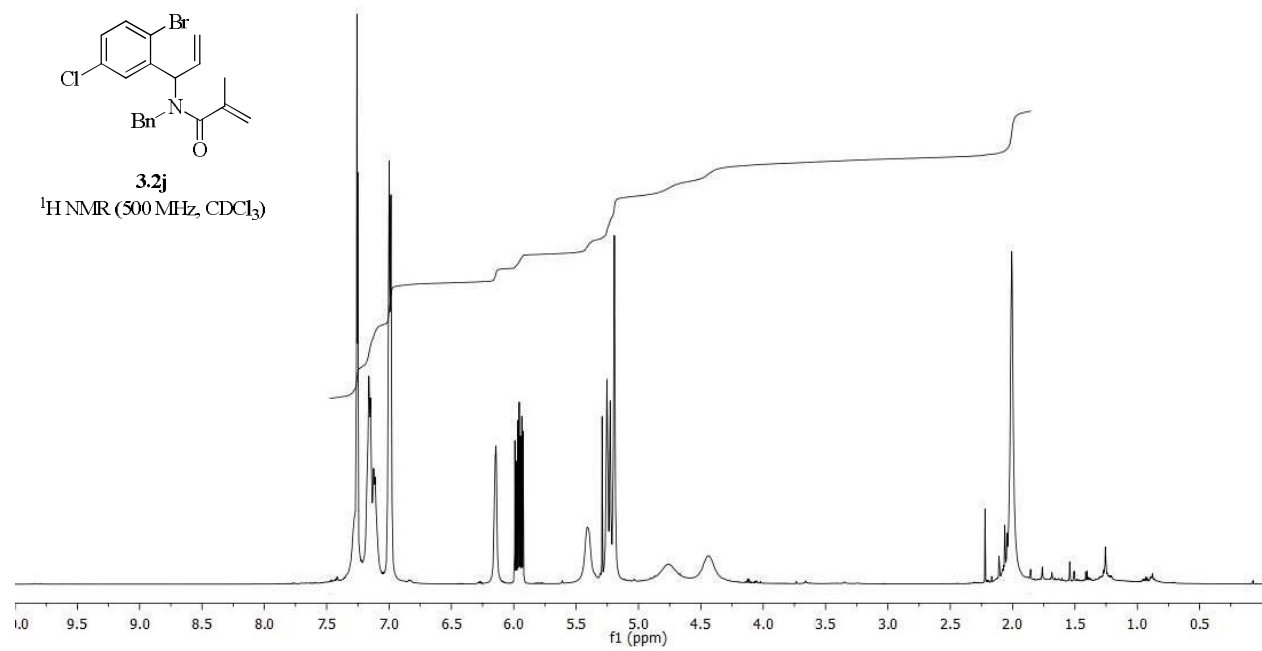
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )

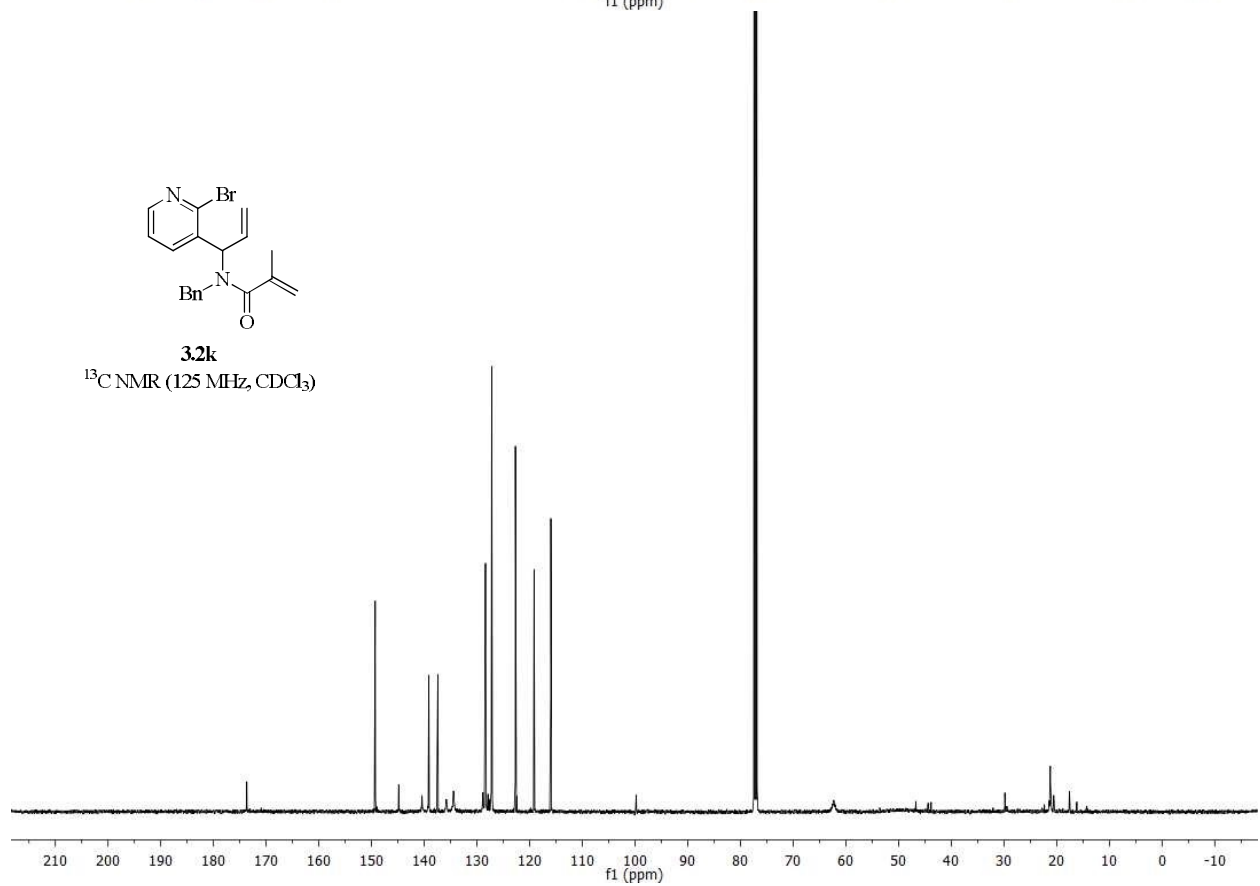
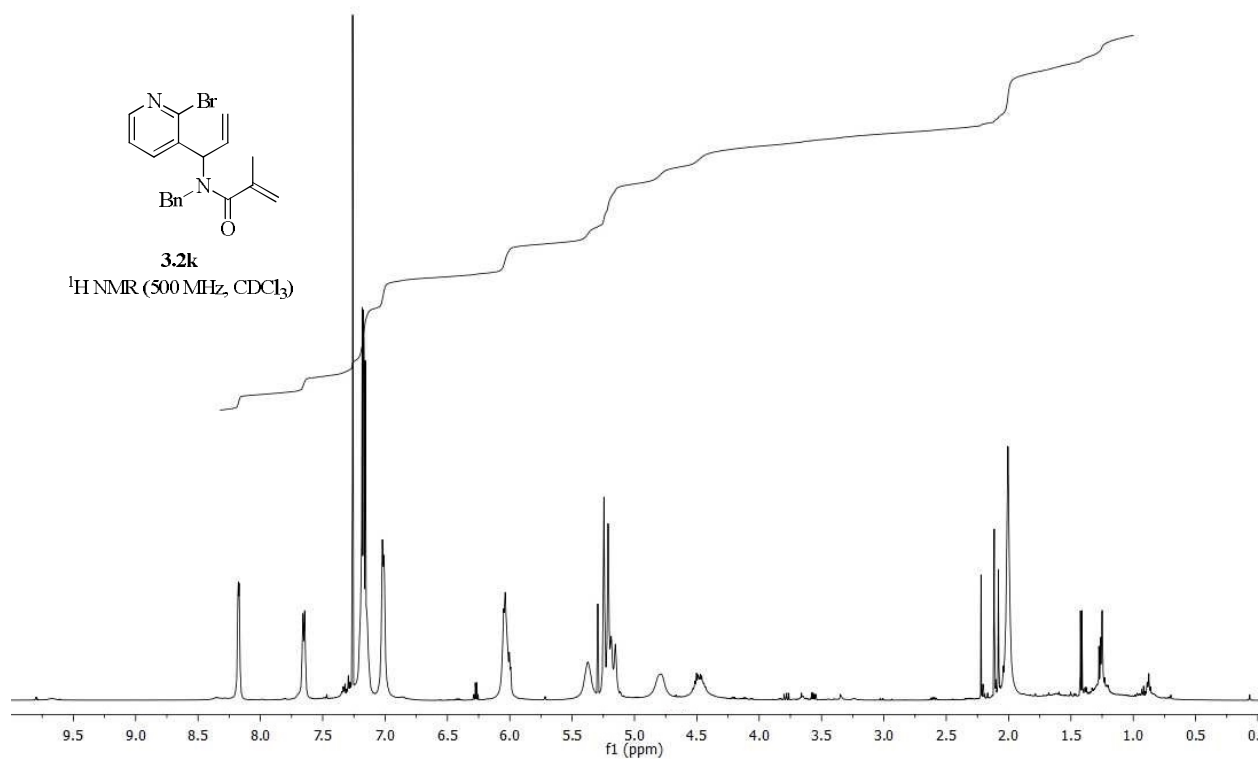




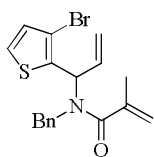






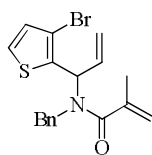
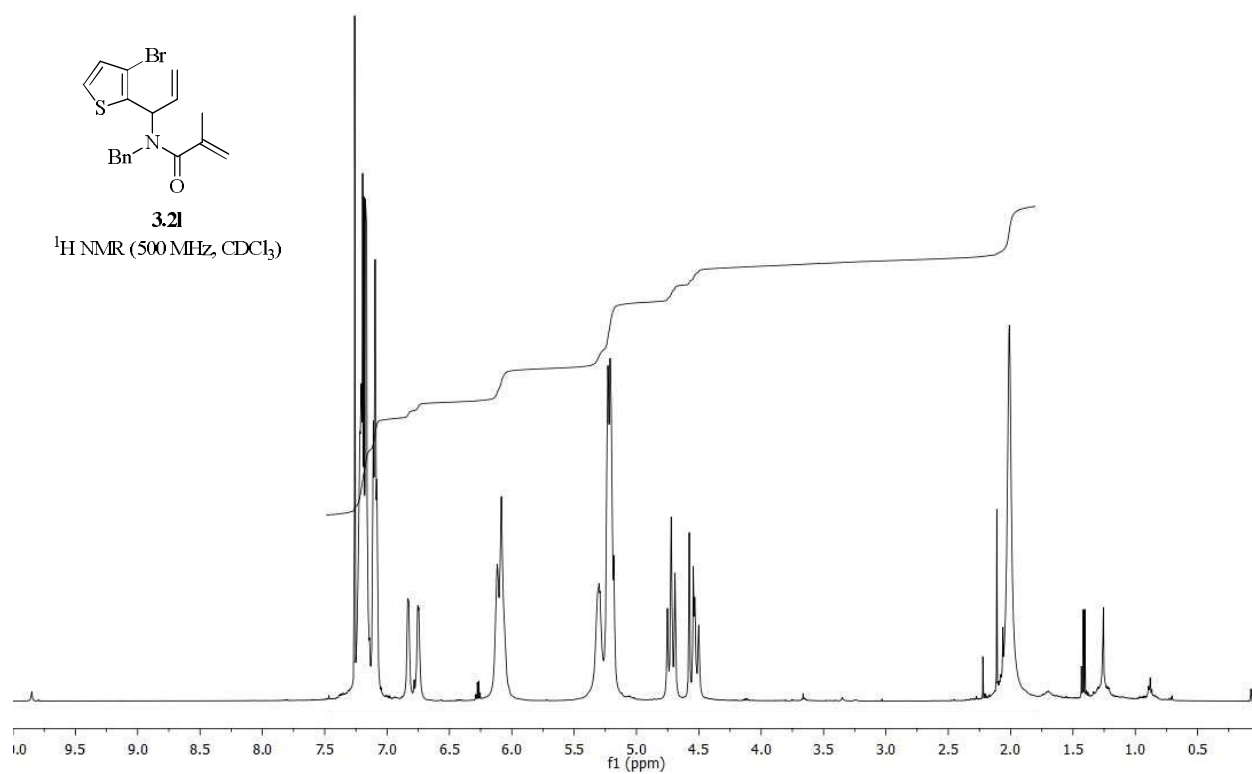






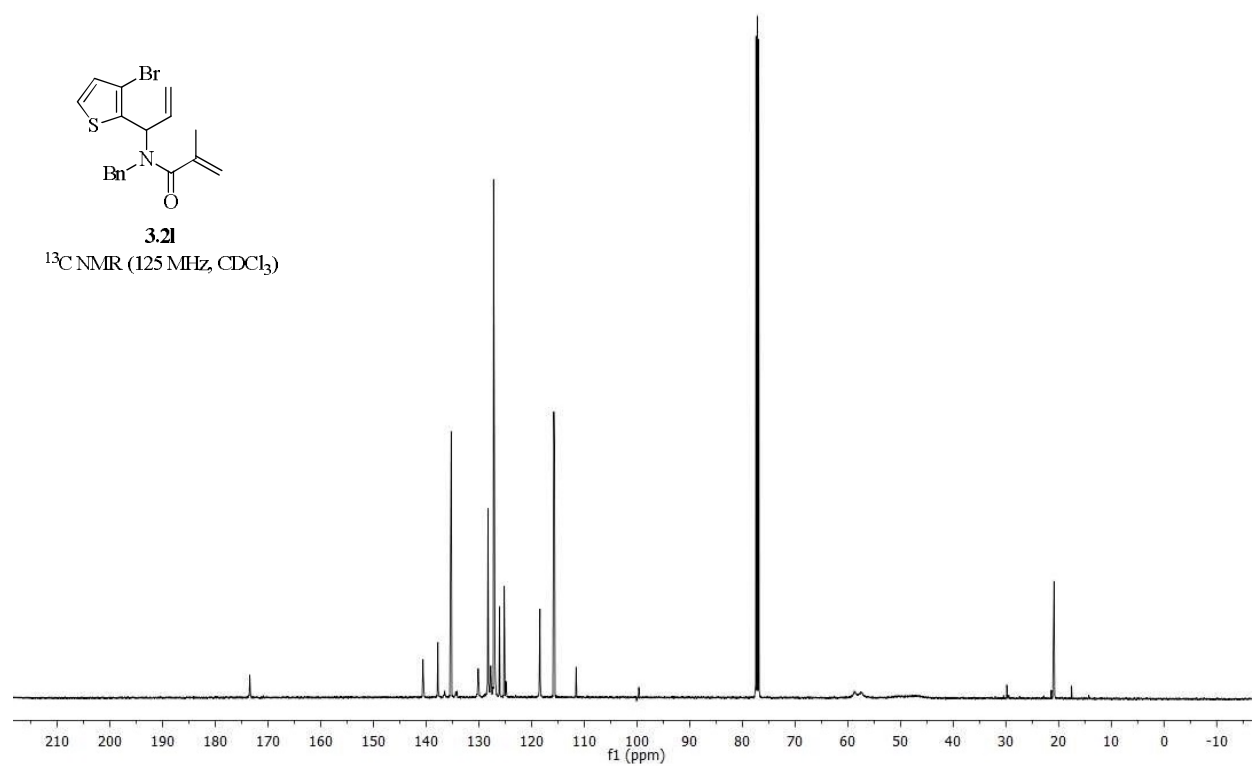
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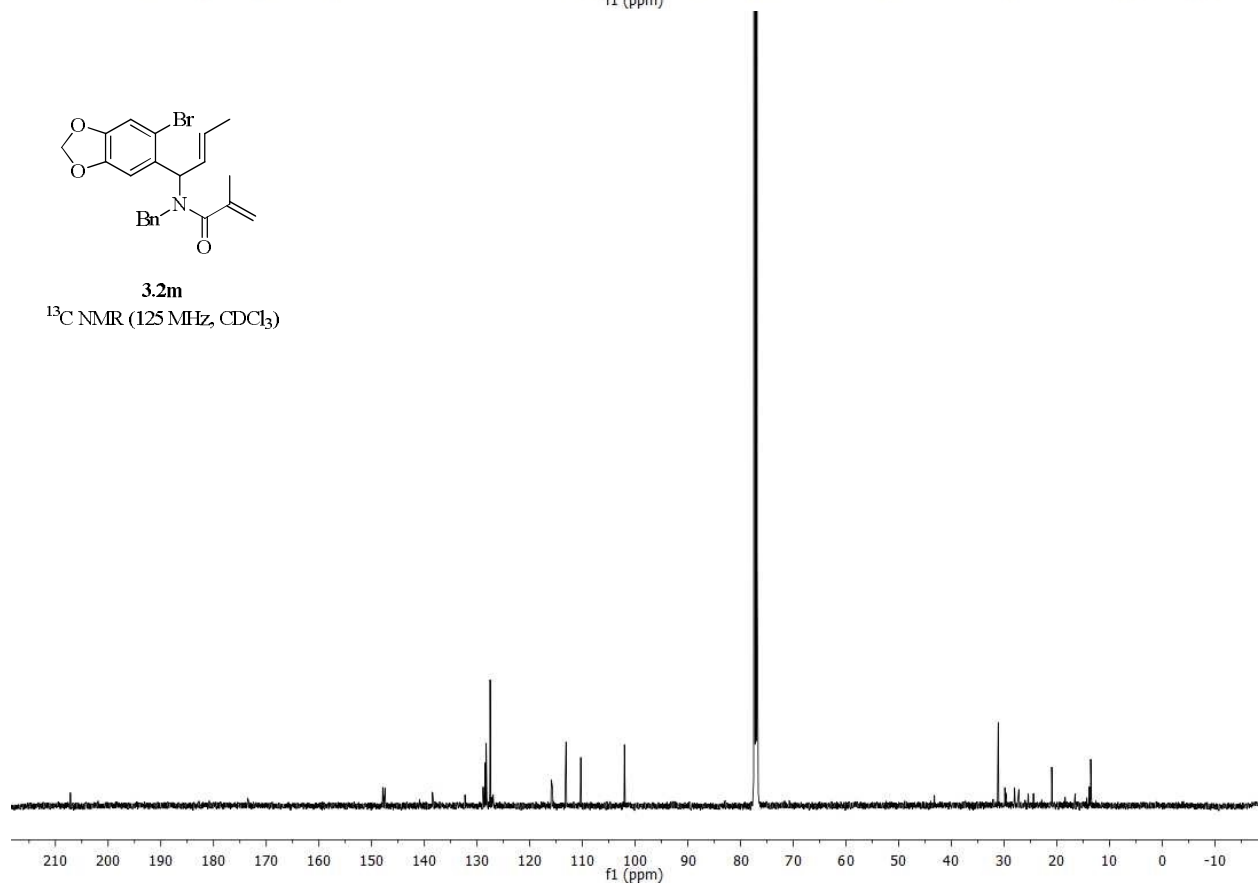
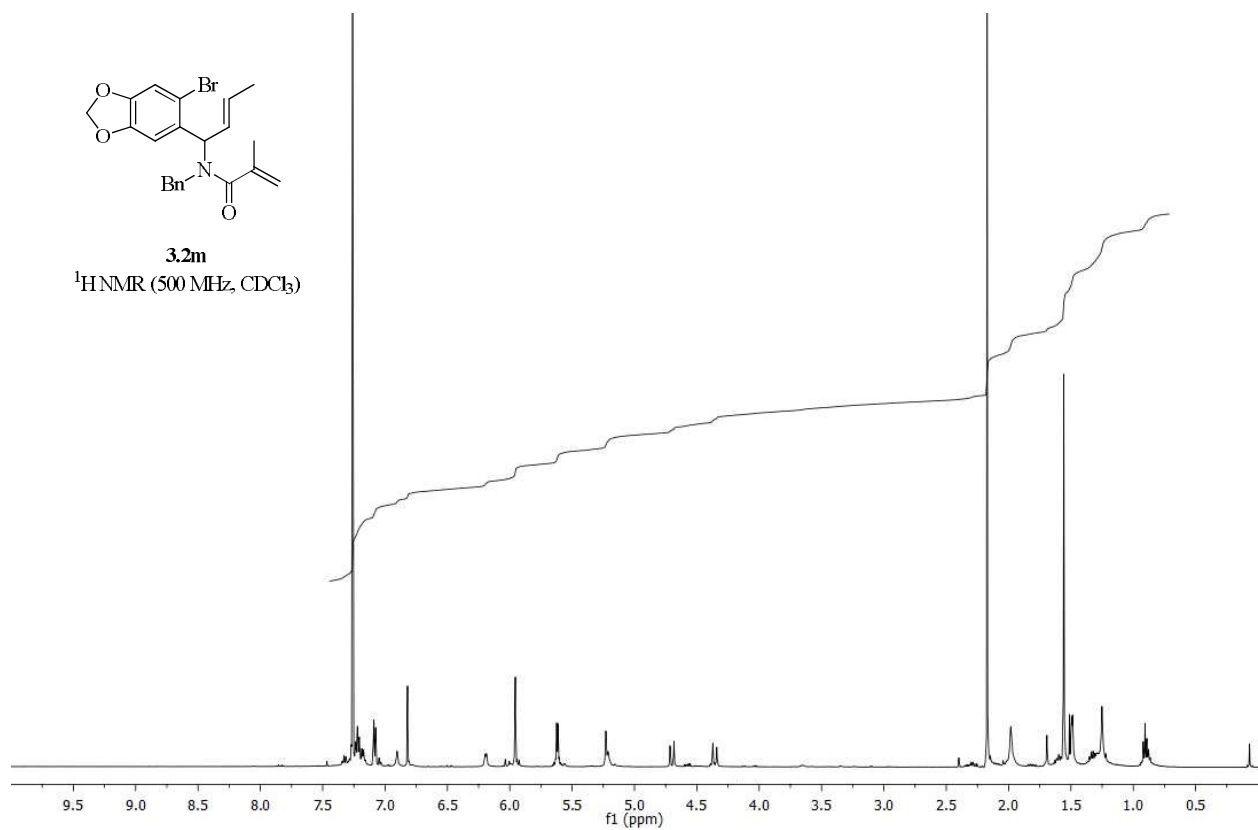
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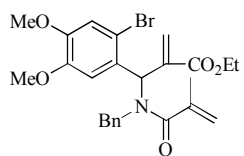


**3.2l**

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)

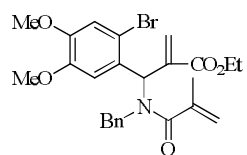
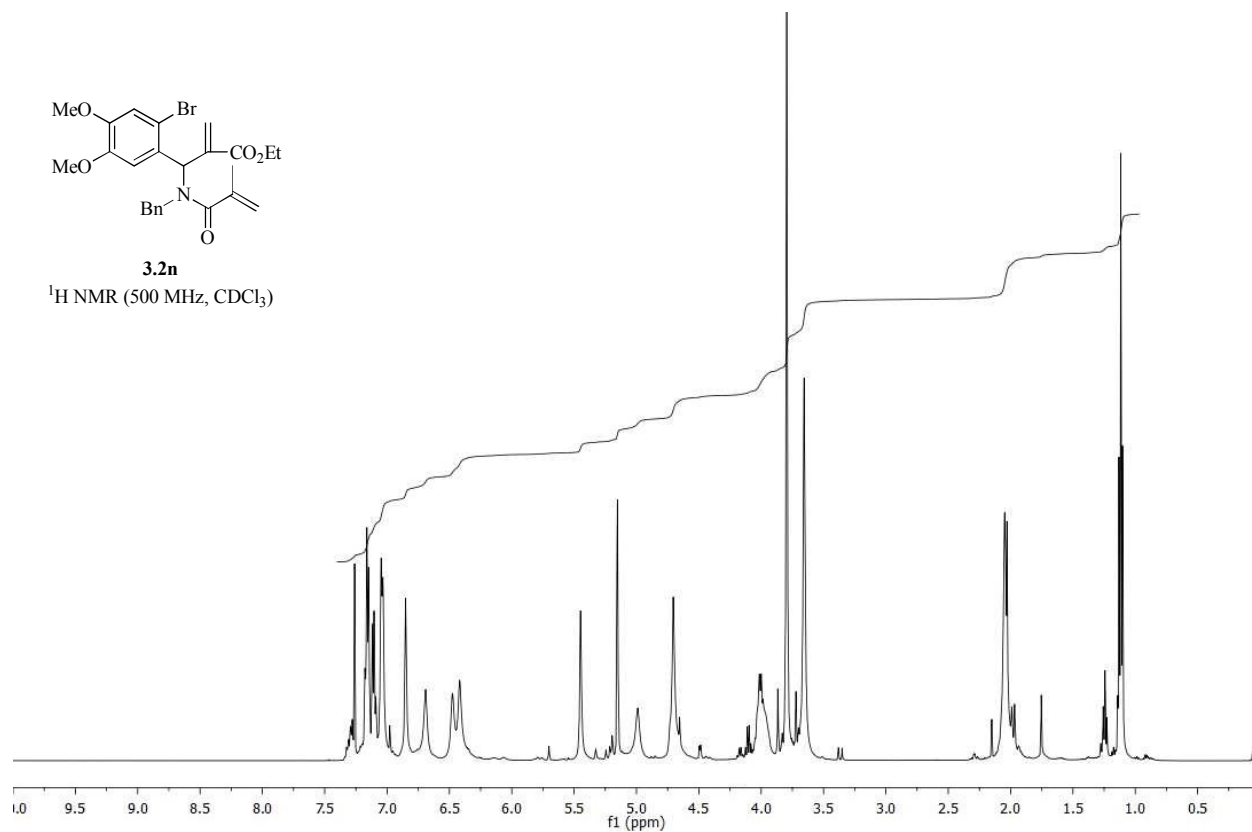






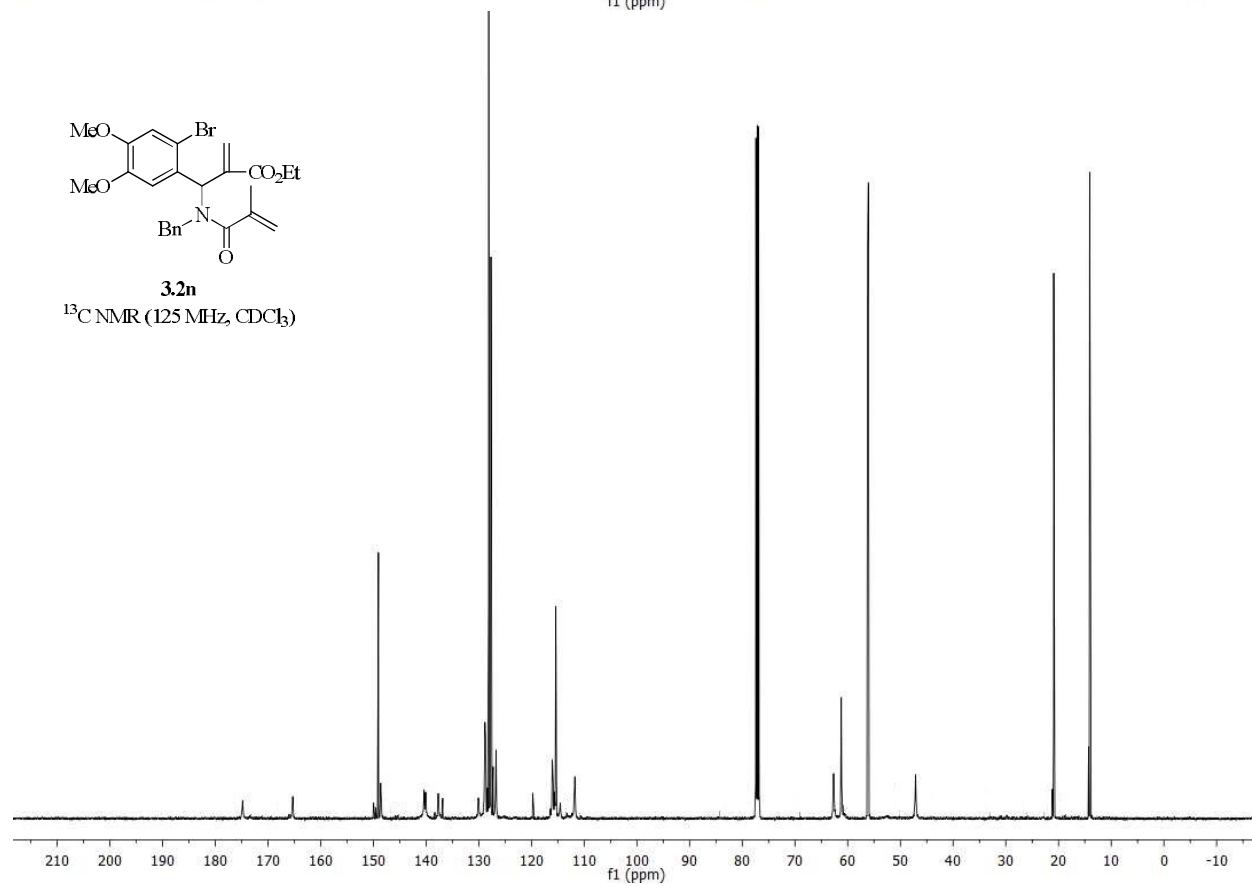
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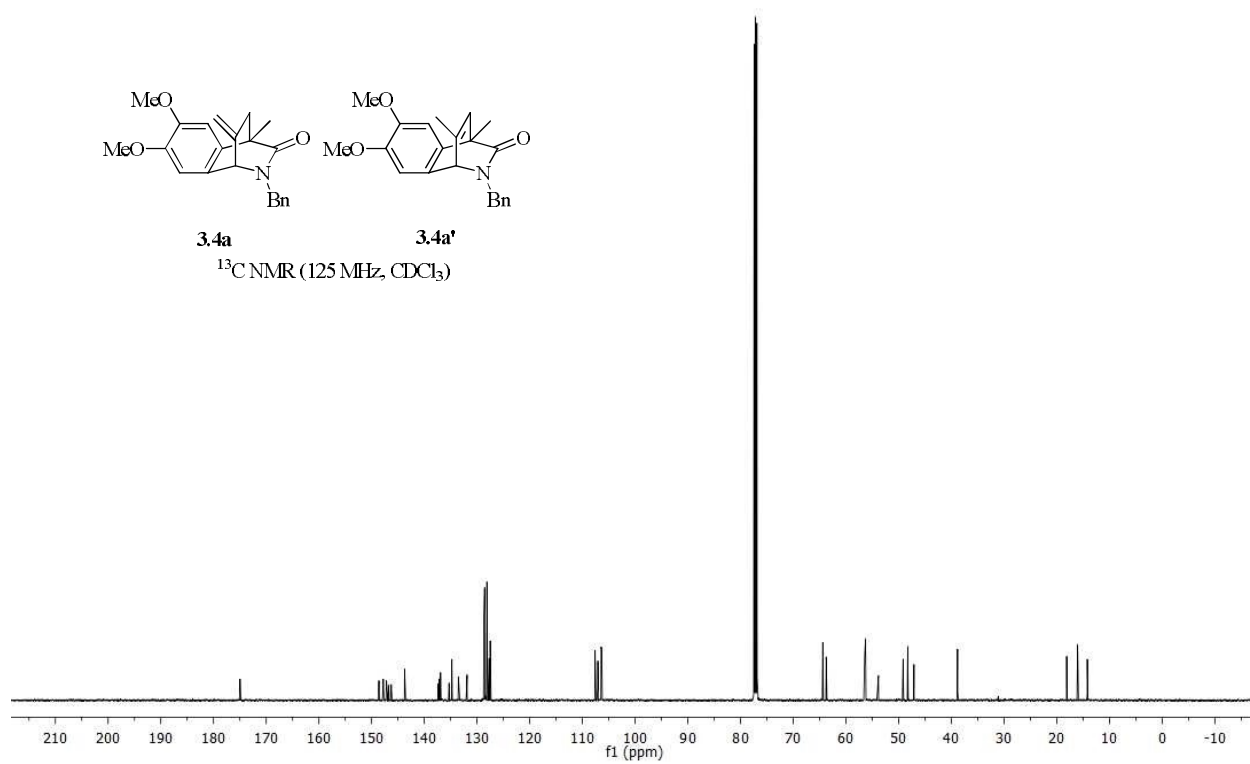
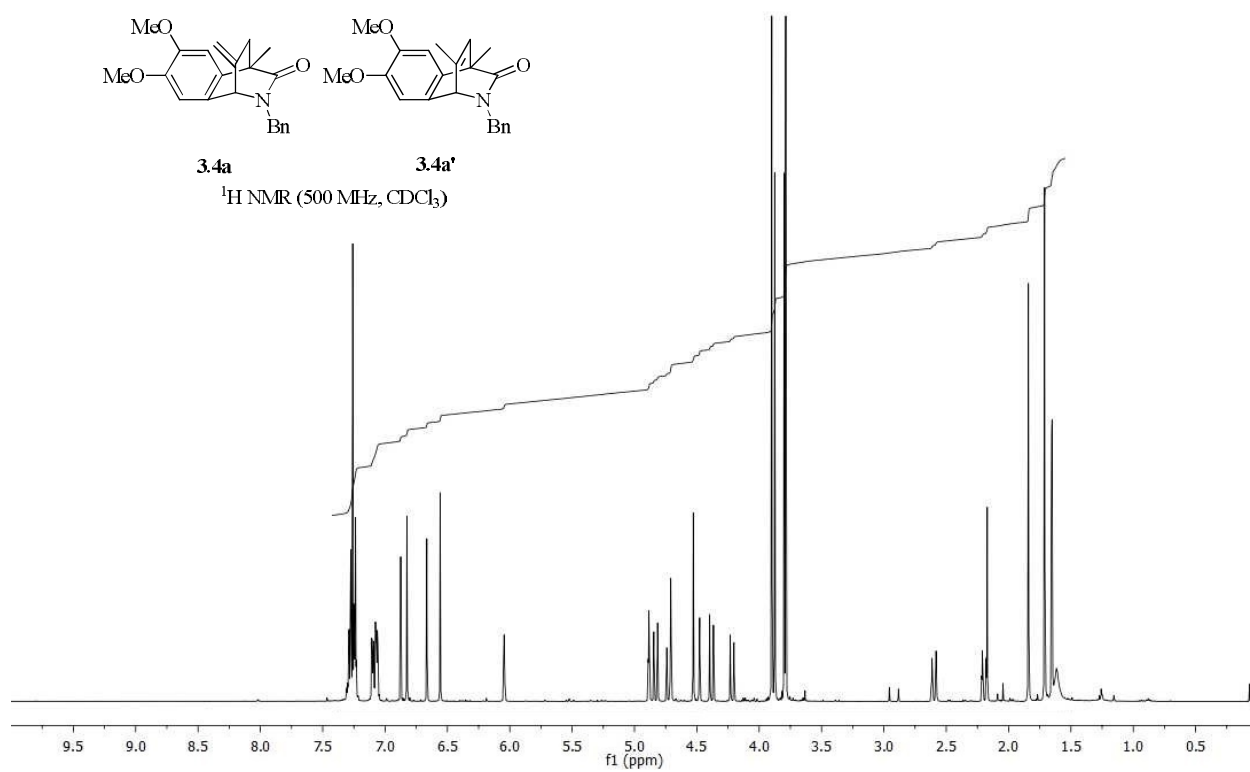
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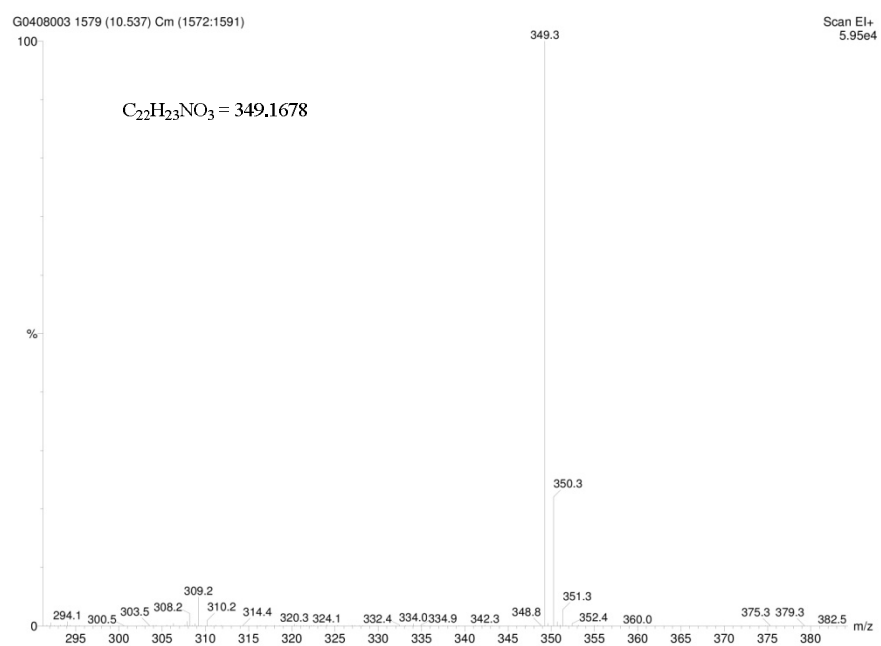
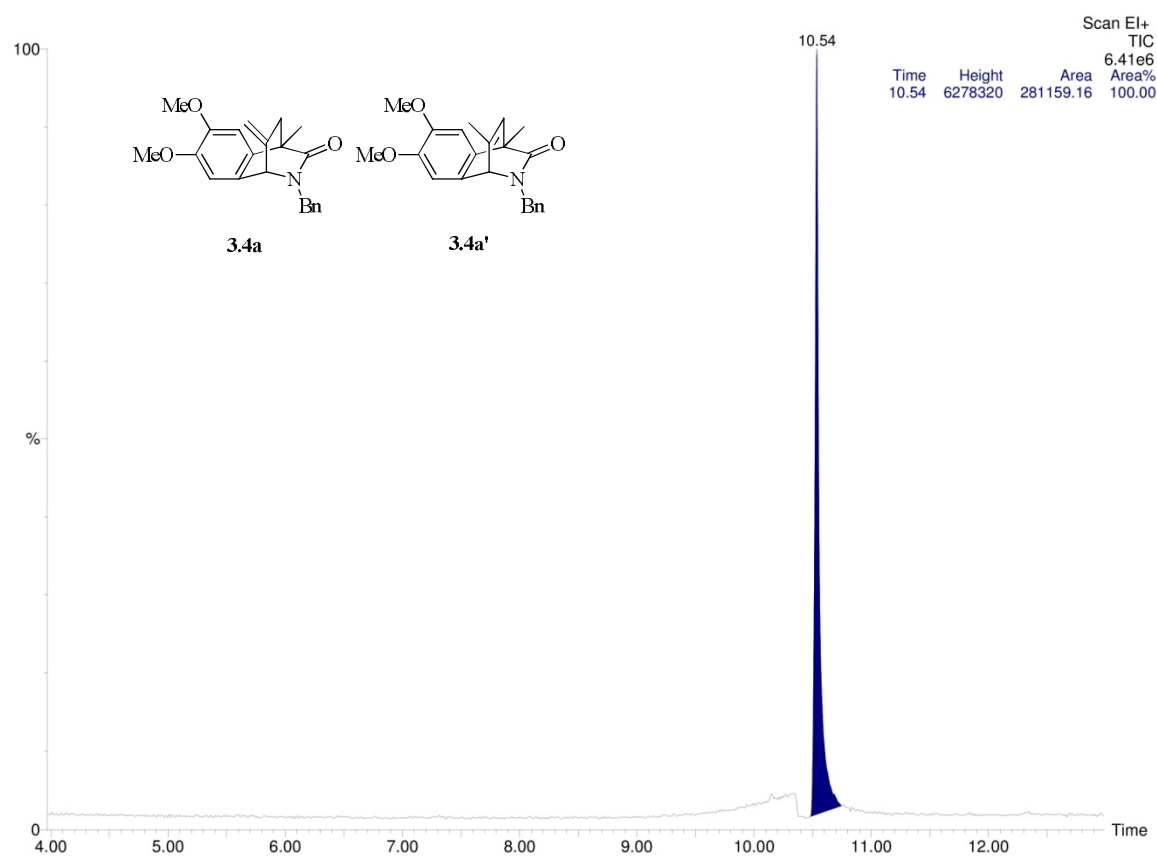


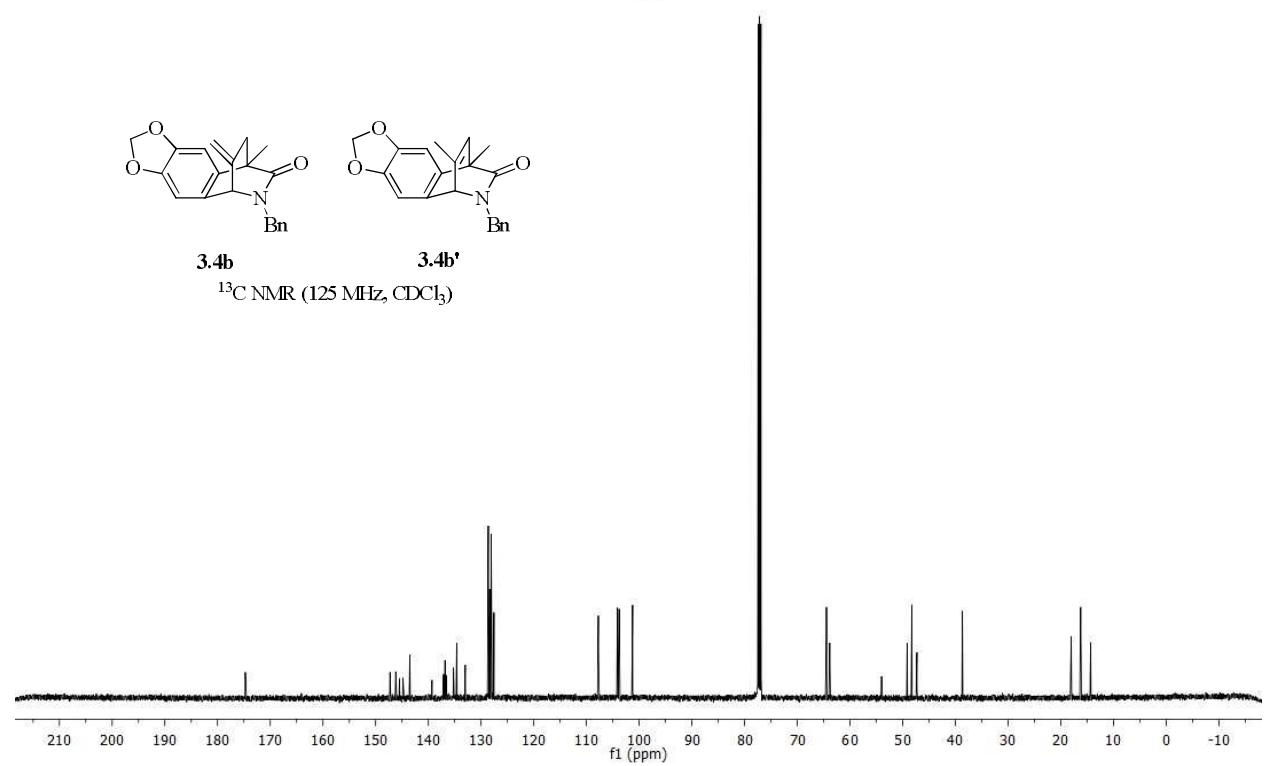
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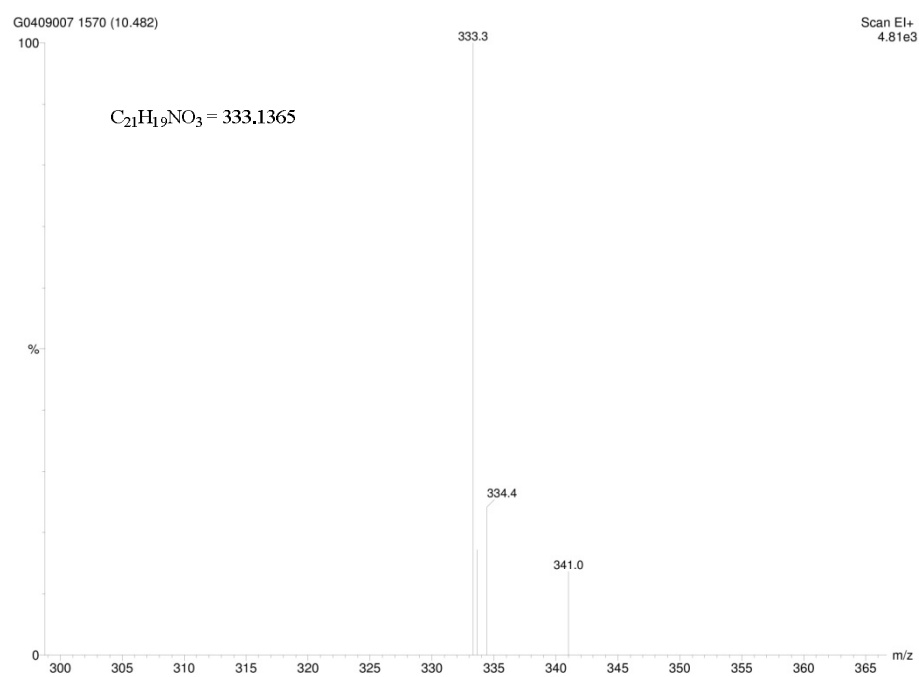
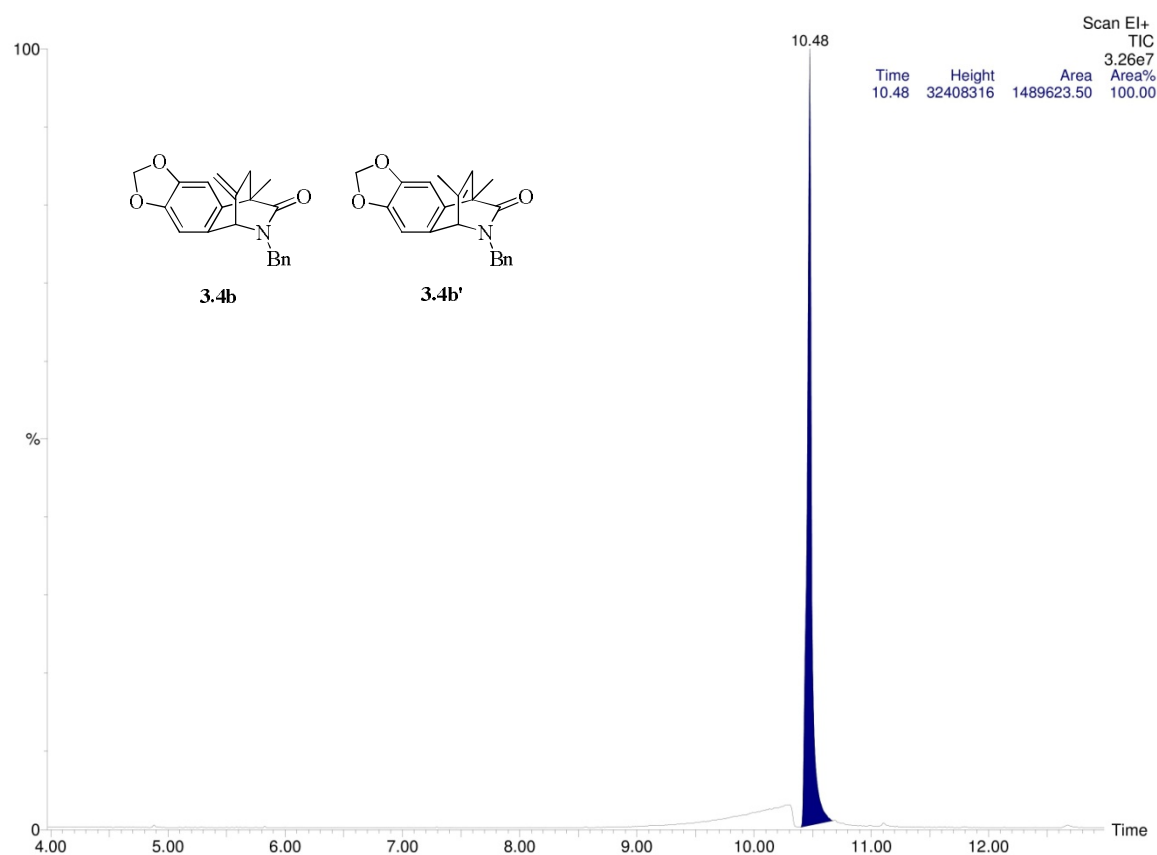
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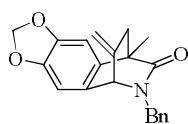






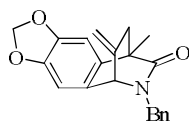
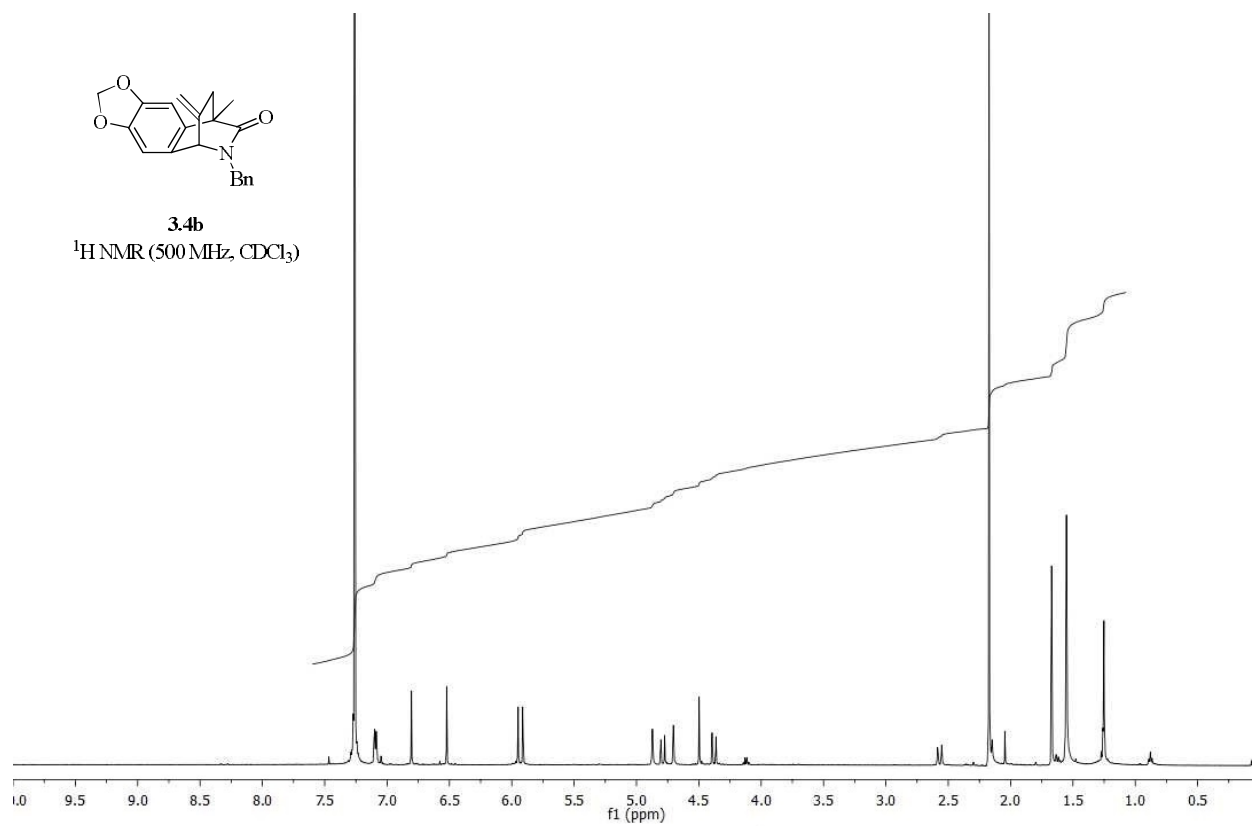






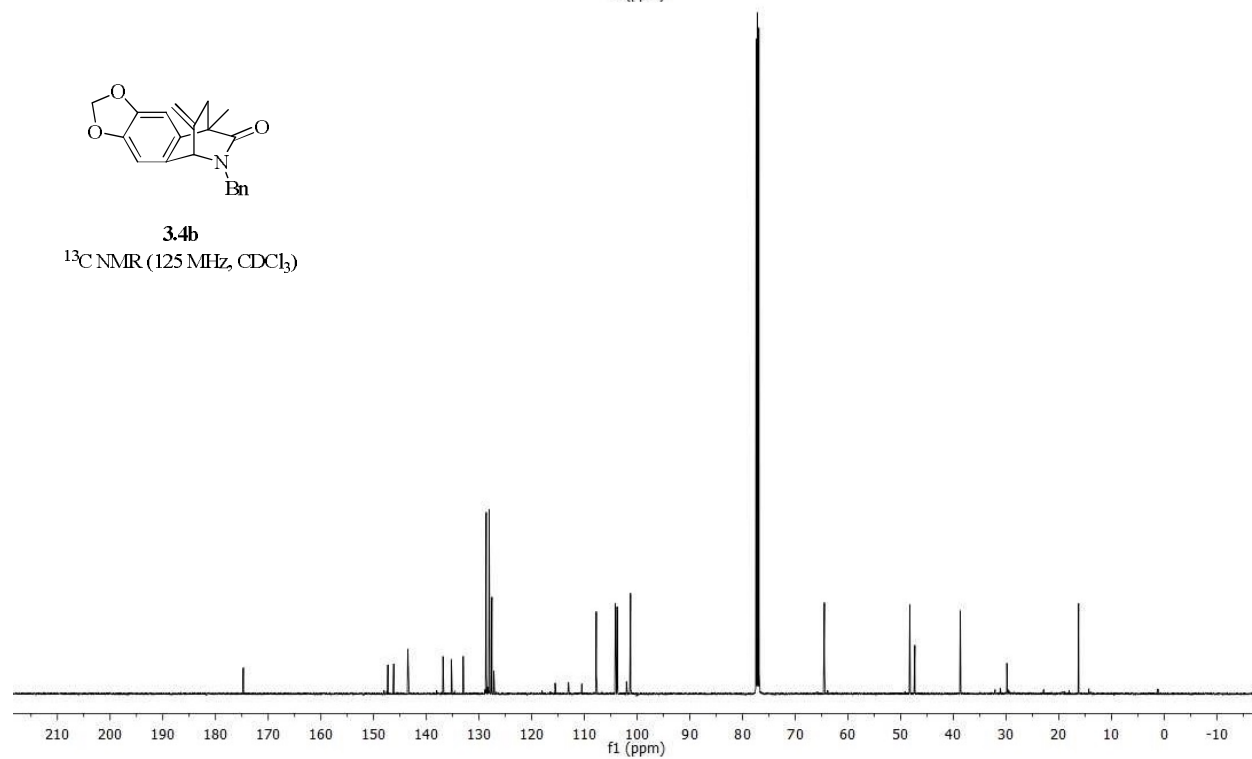
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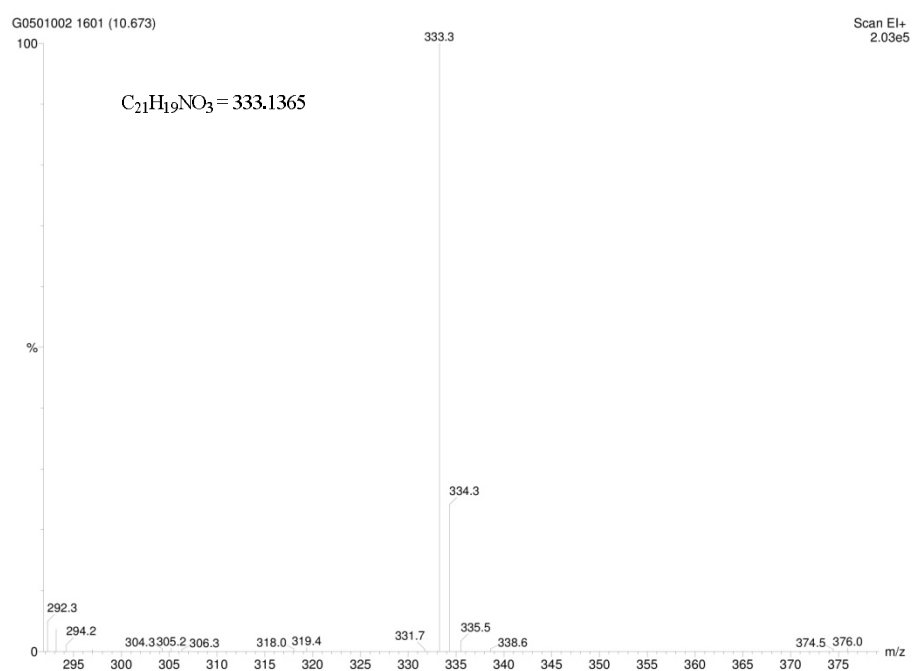
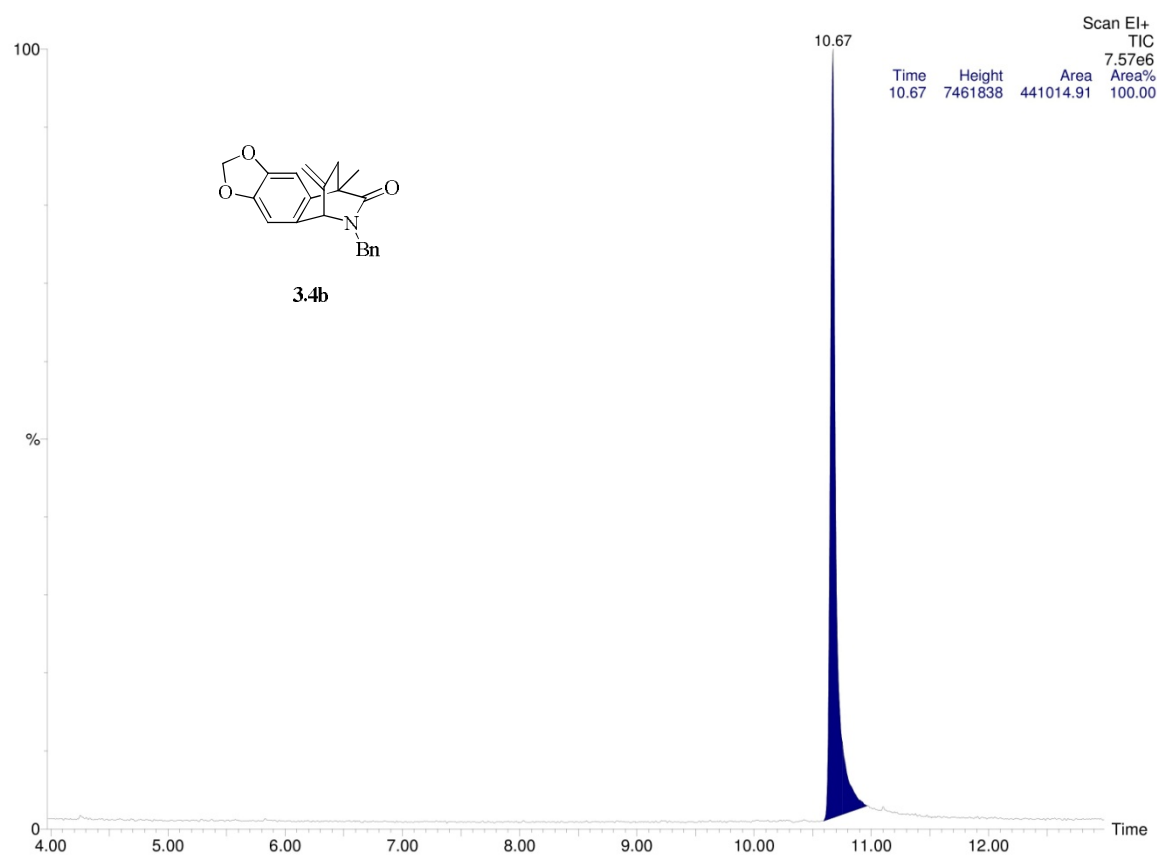


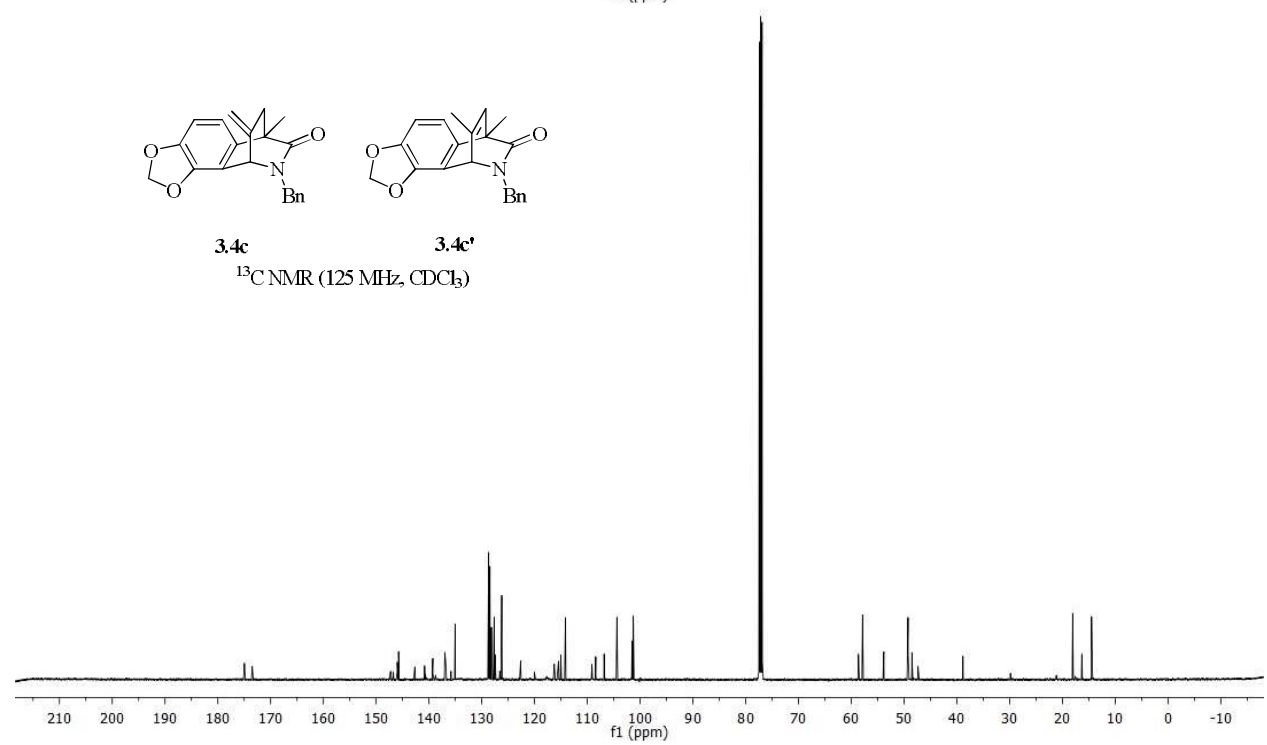
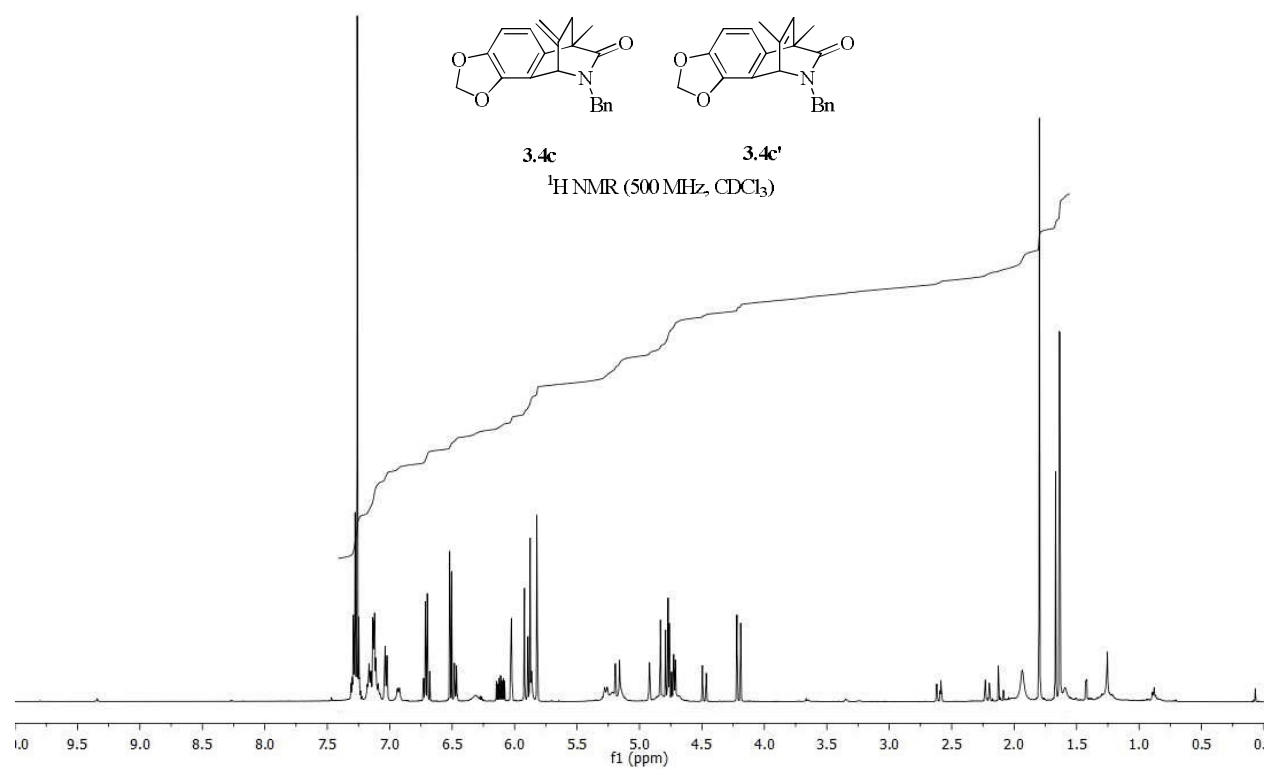
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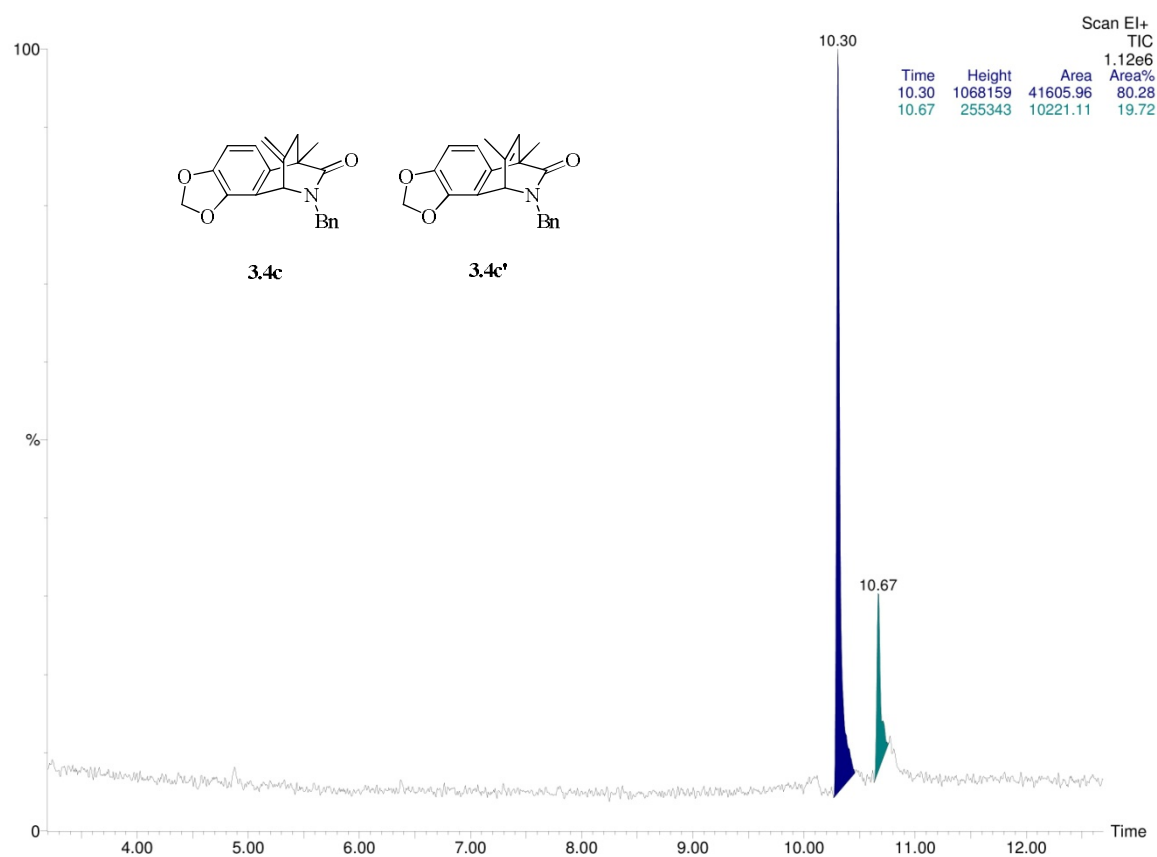
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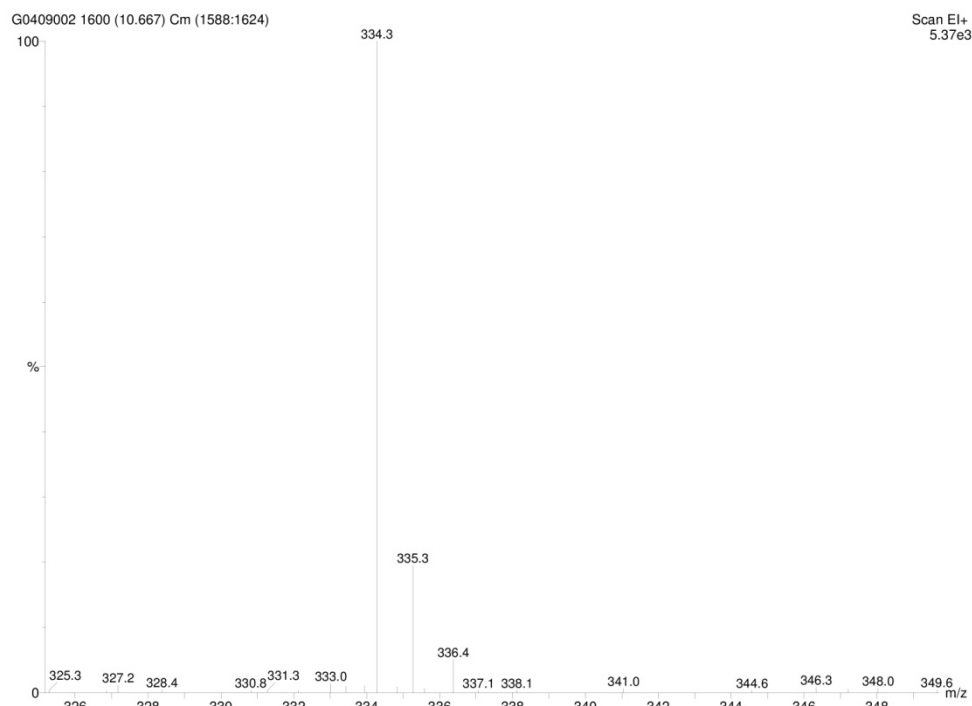
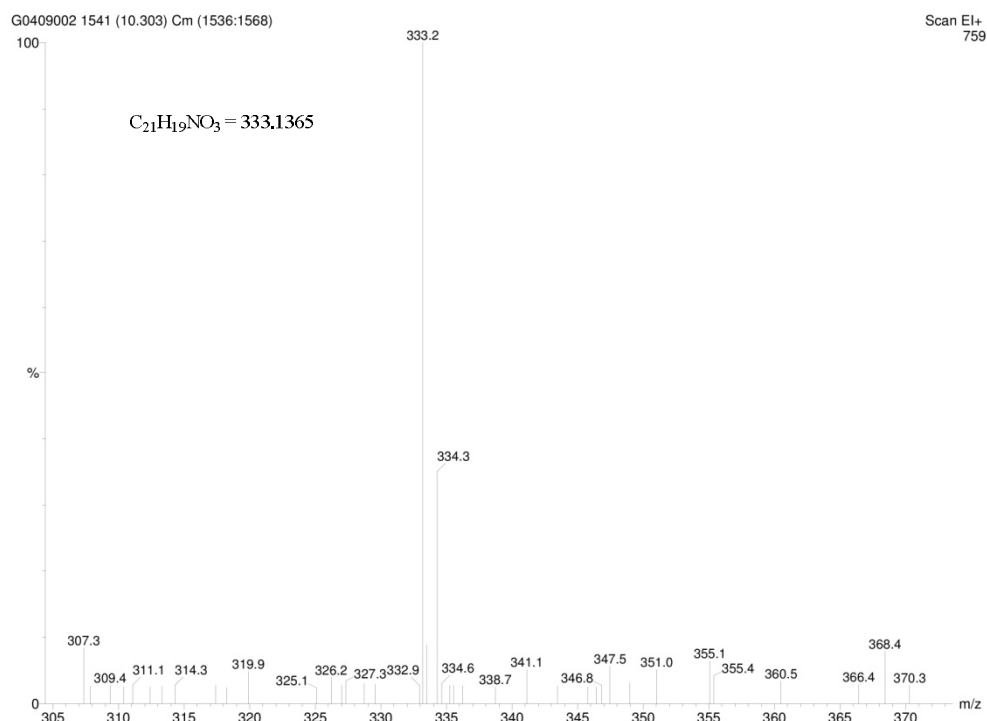


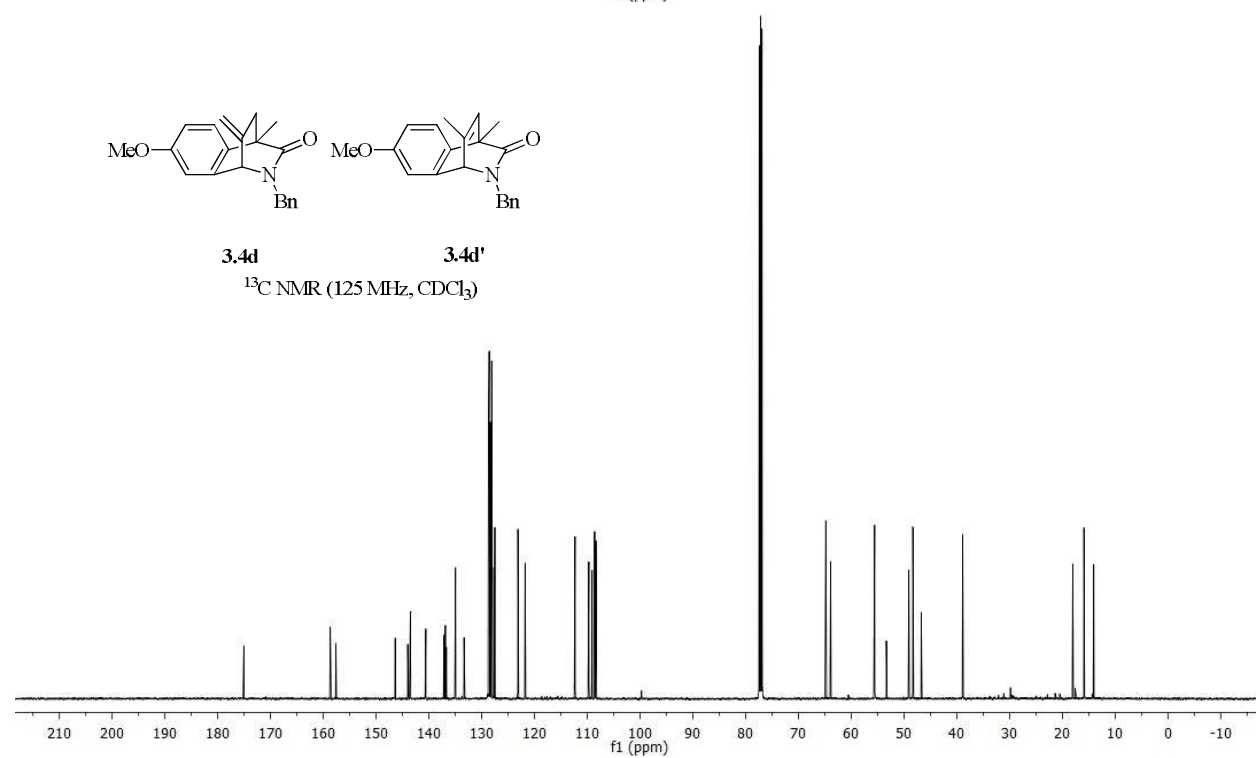
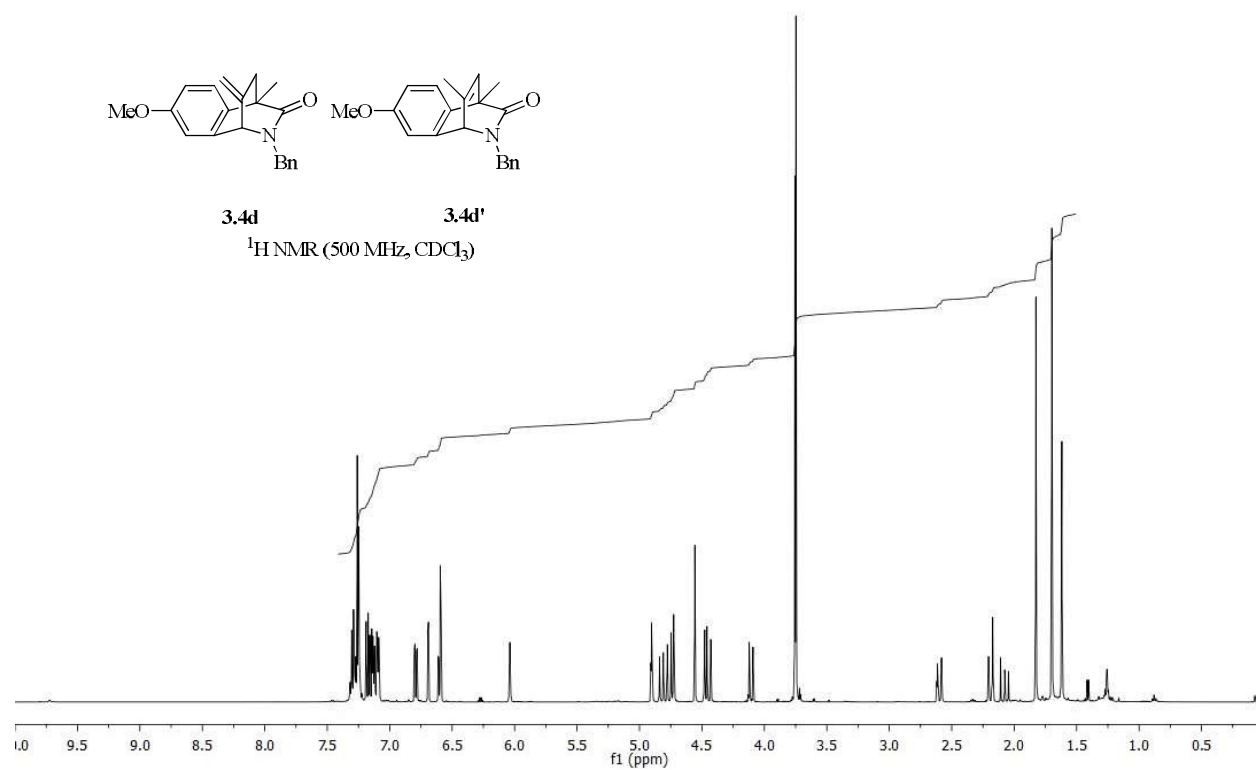


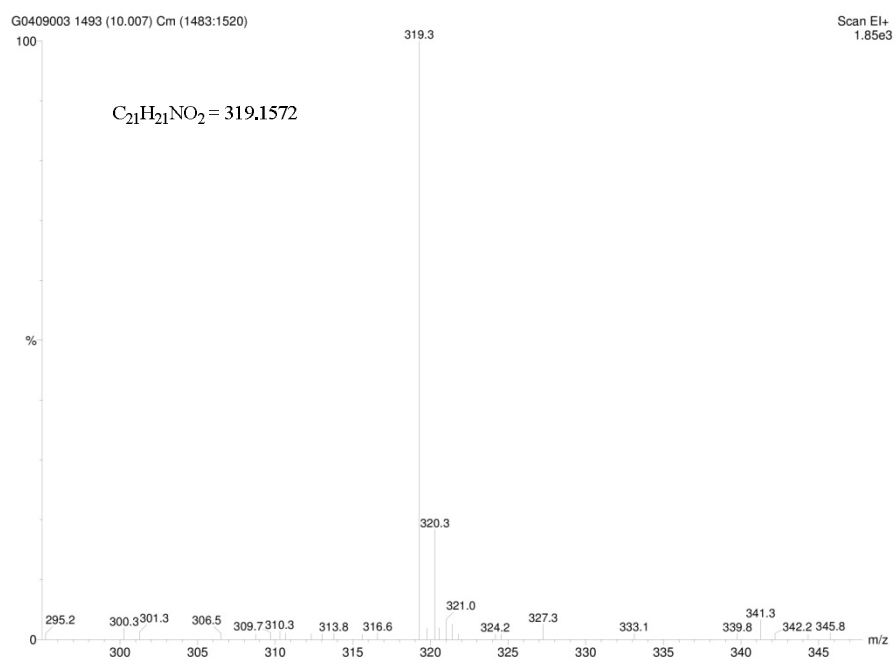
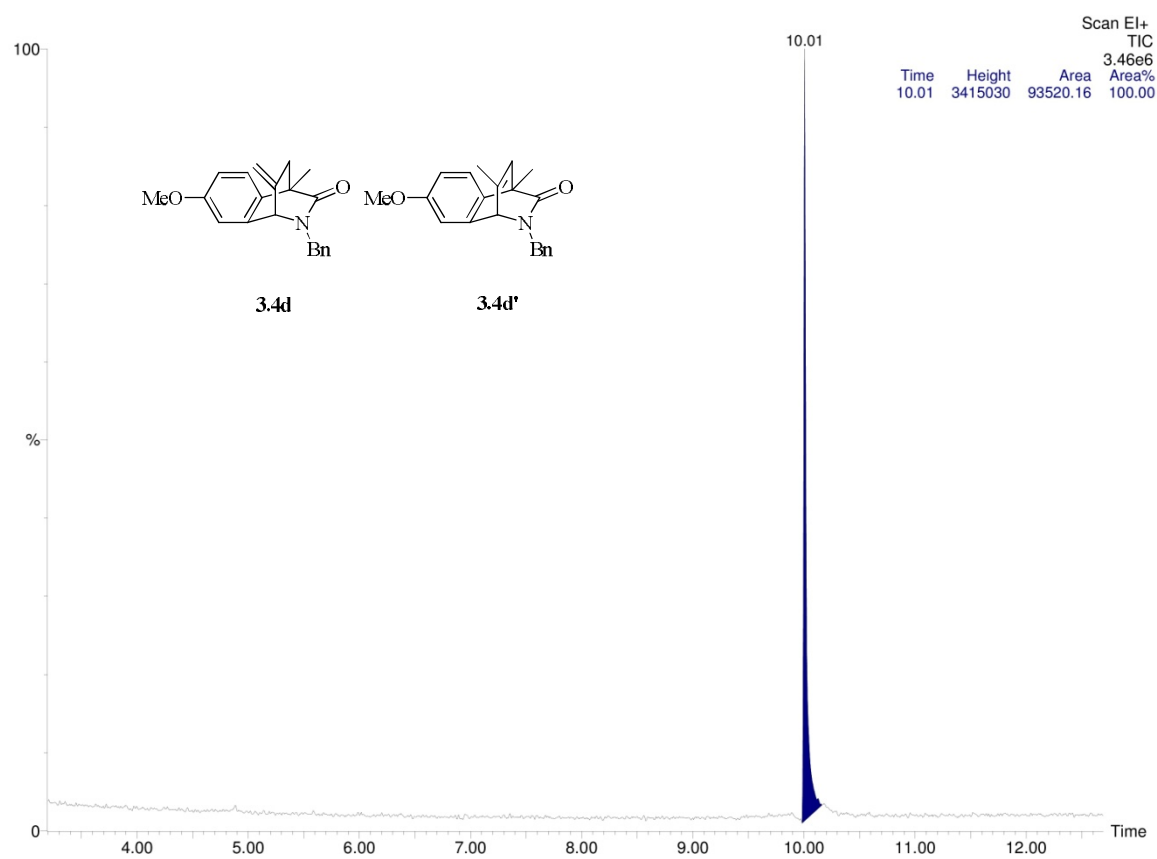


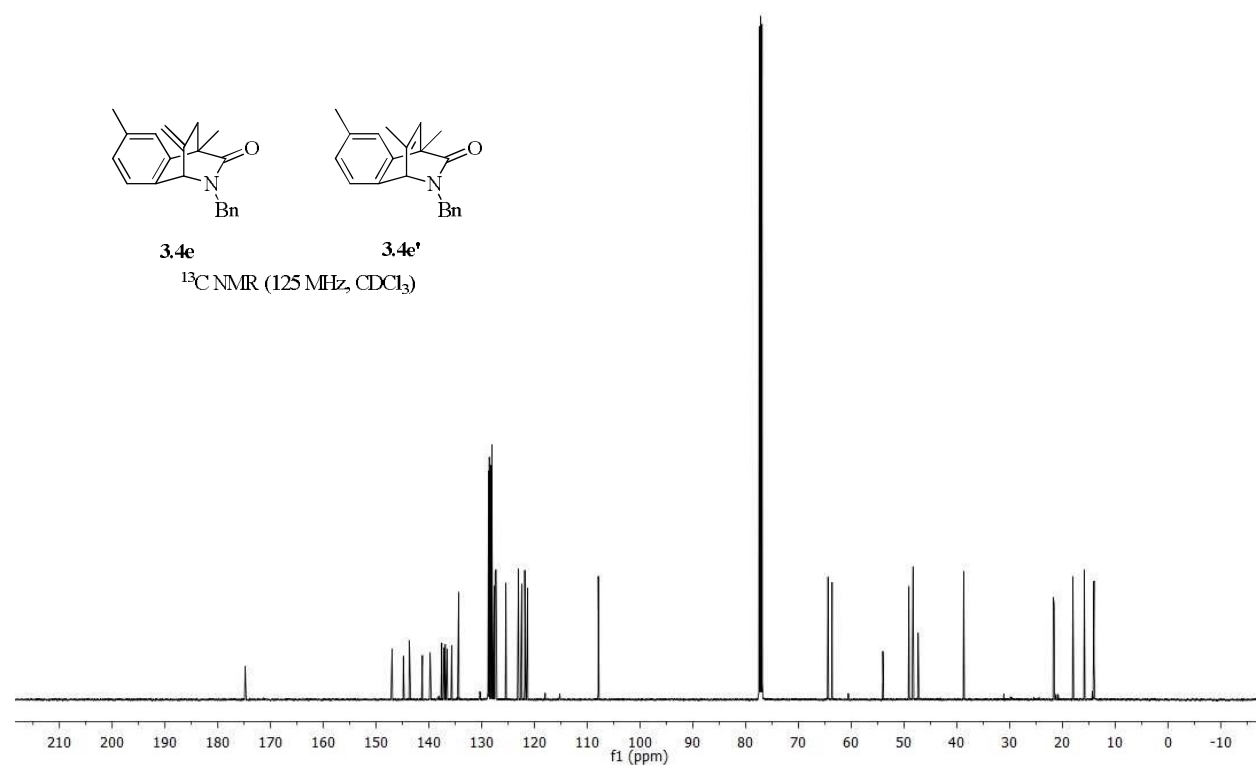
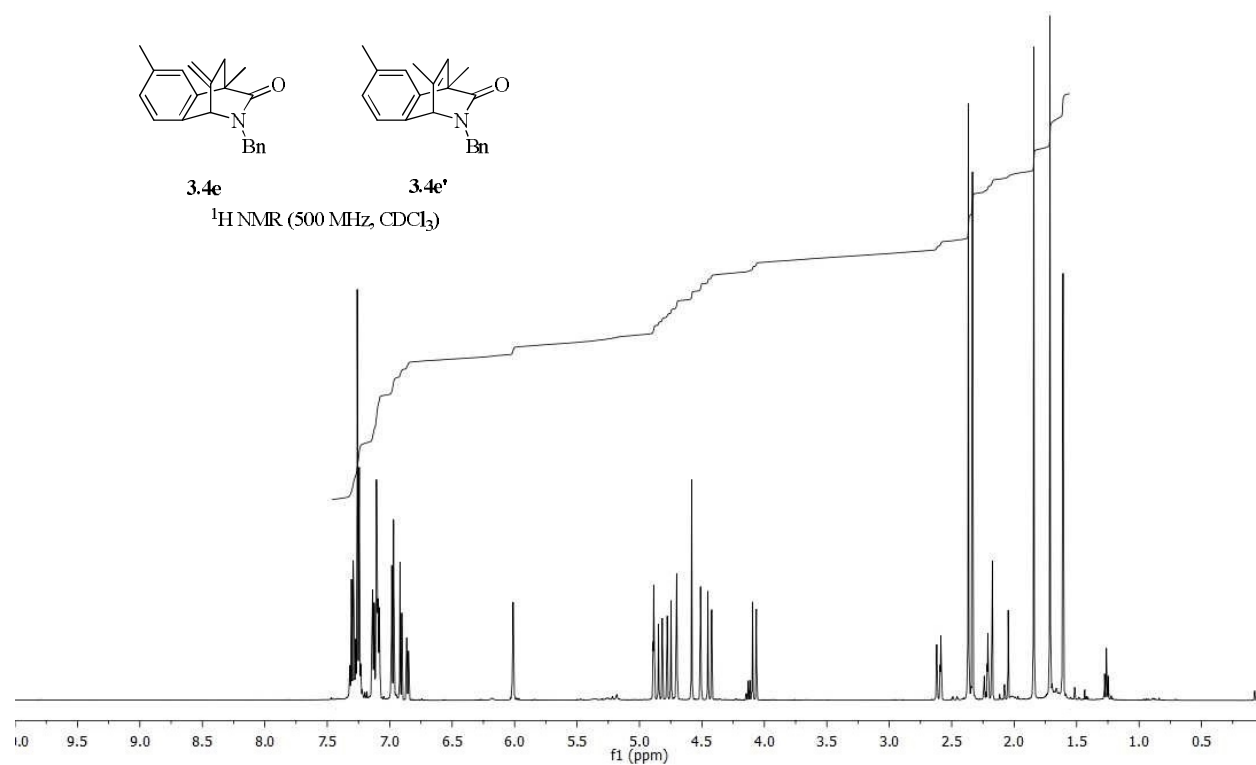


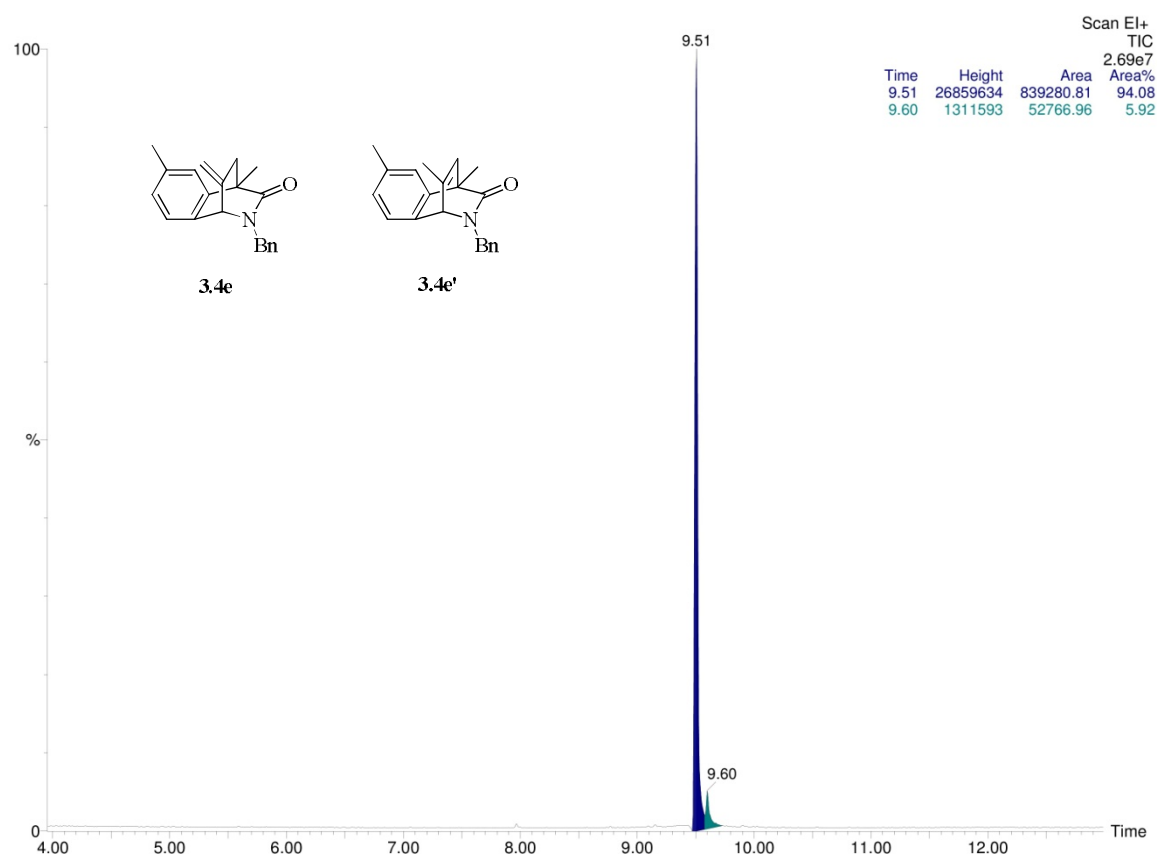




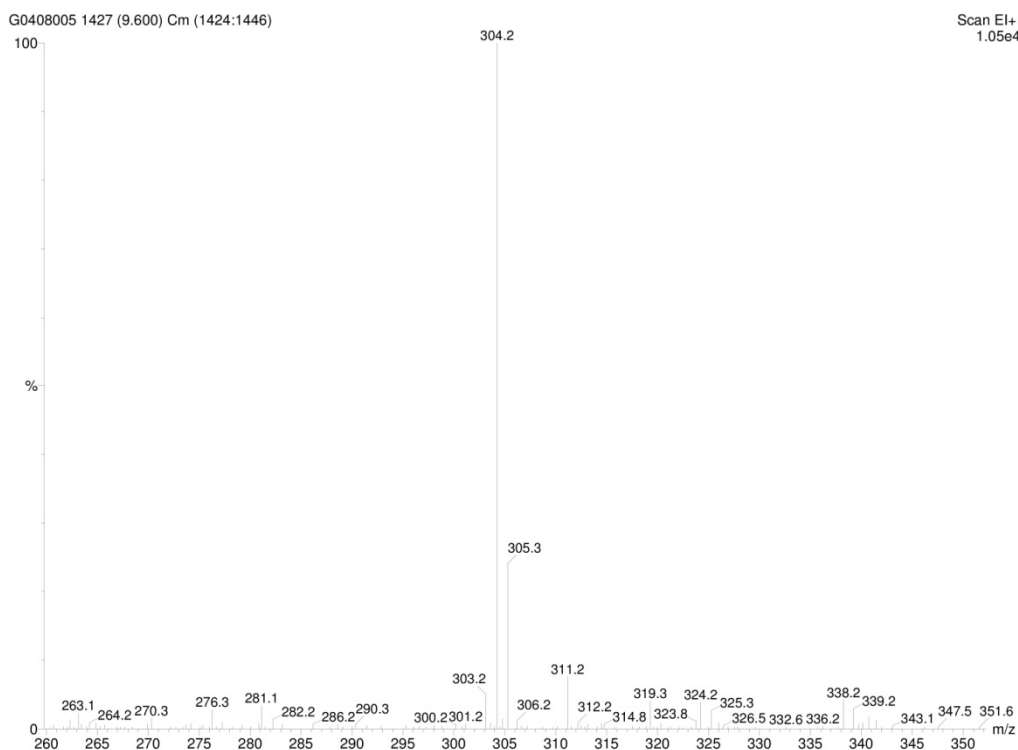
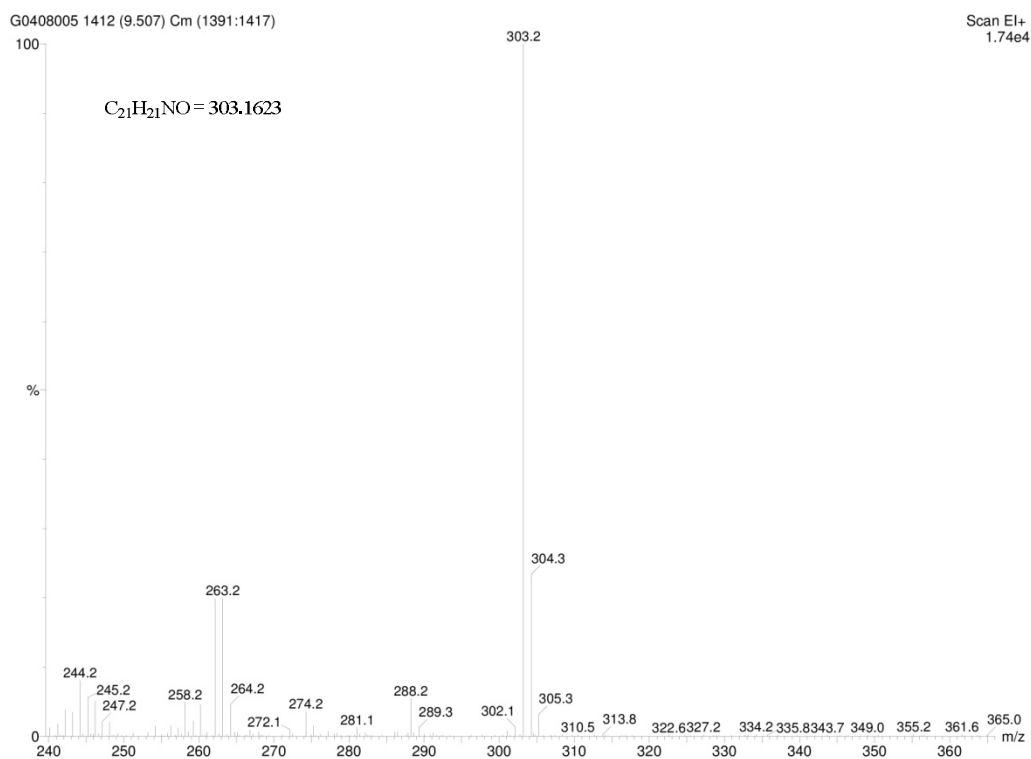


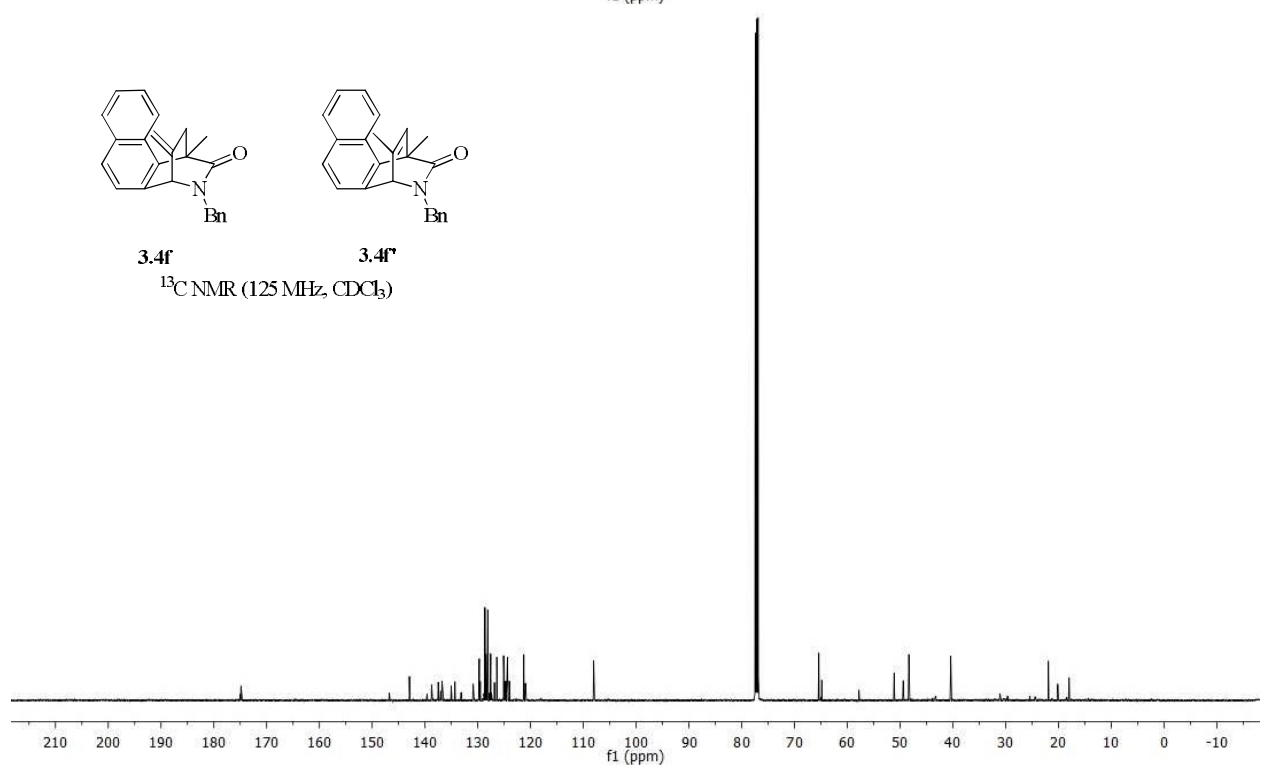
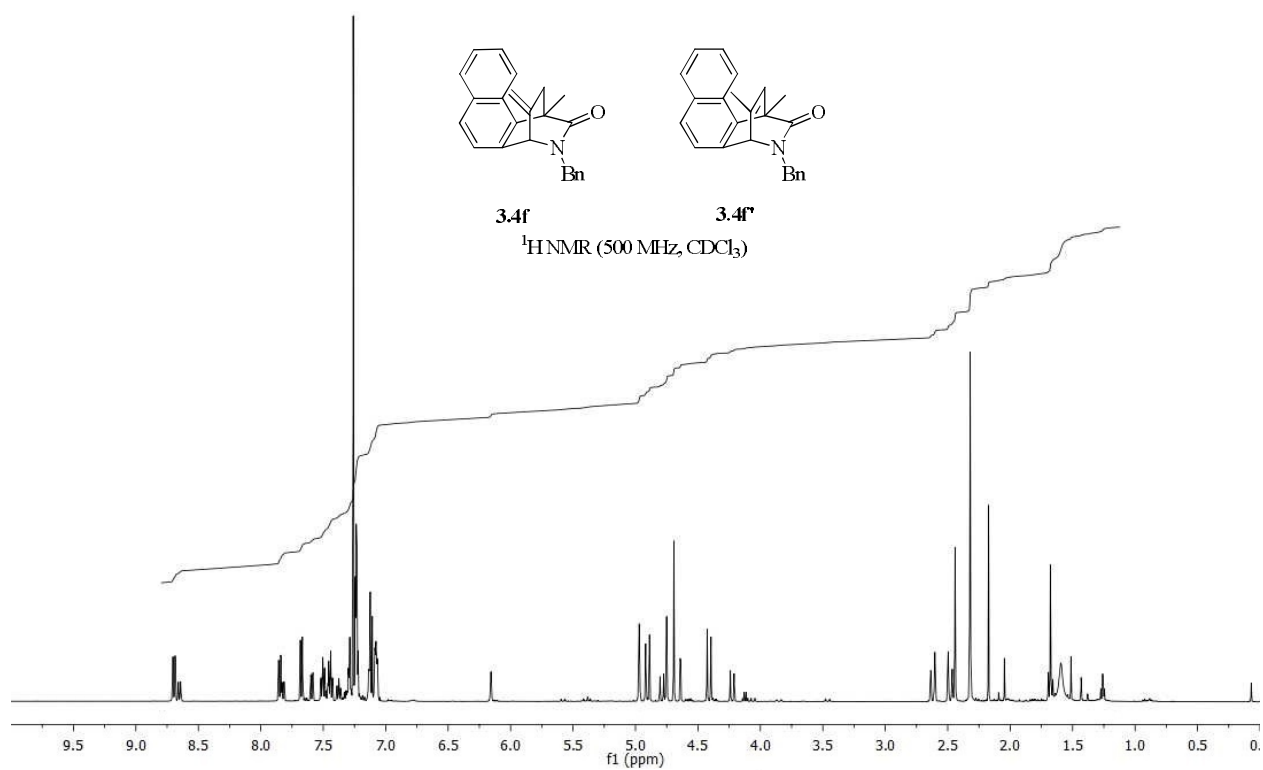


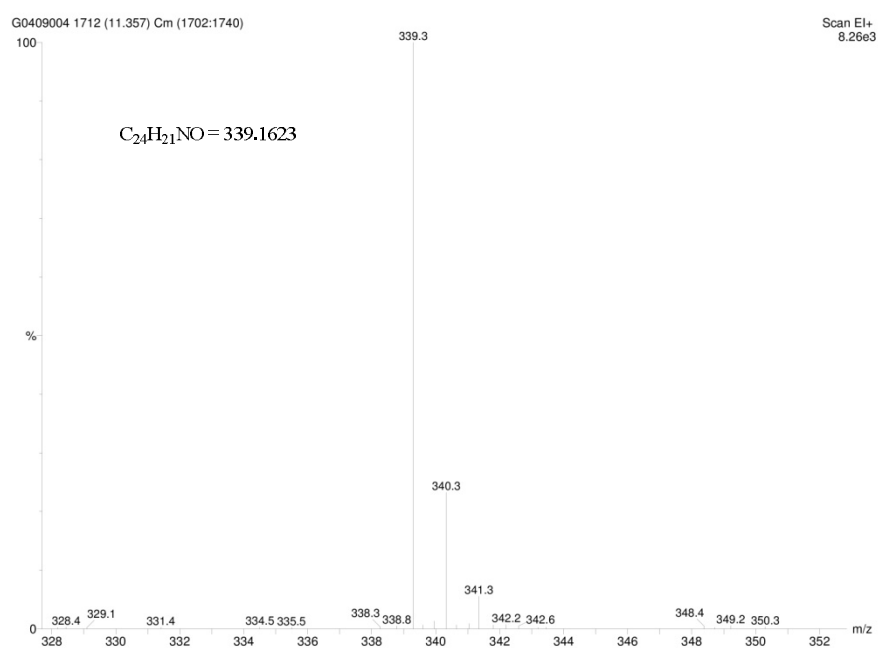
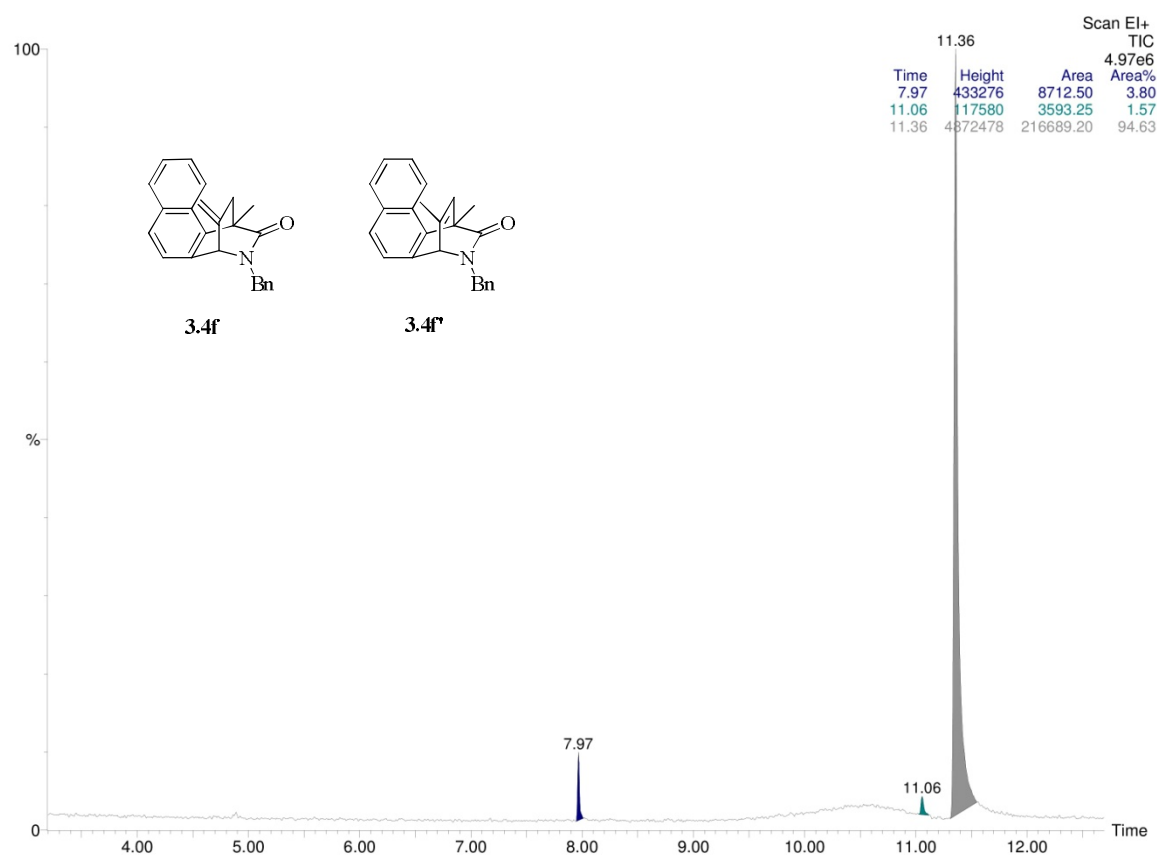


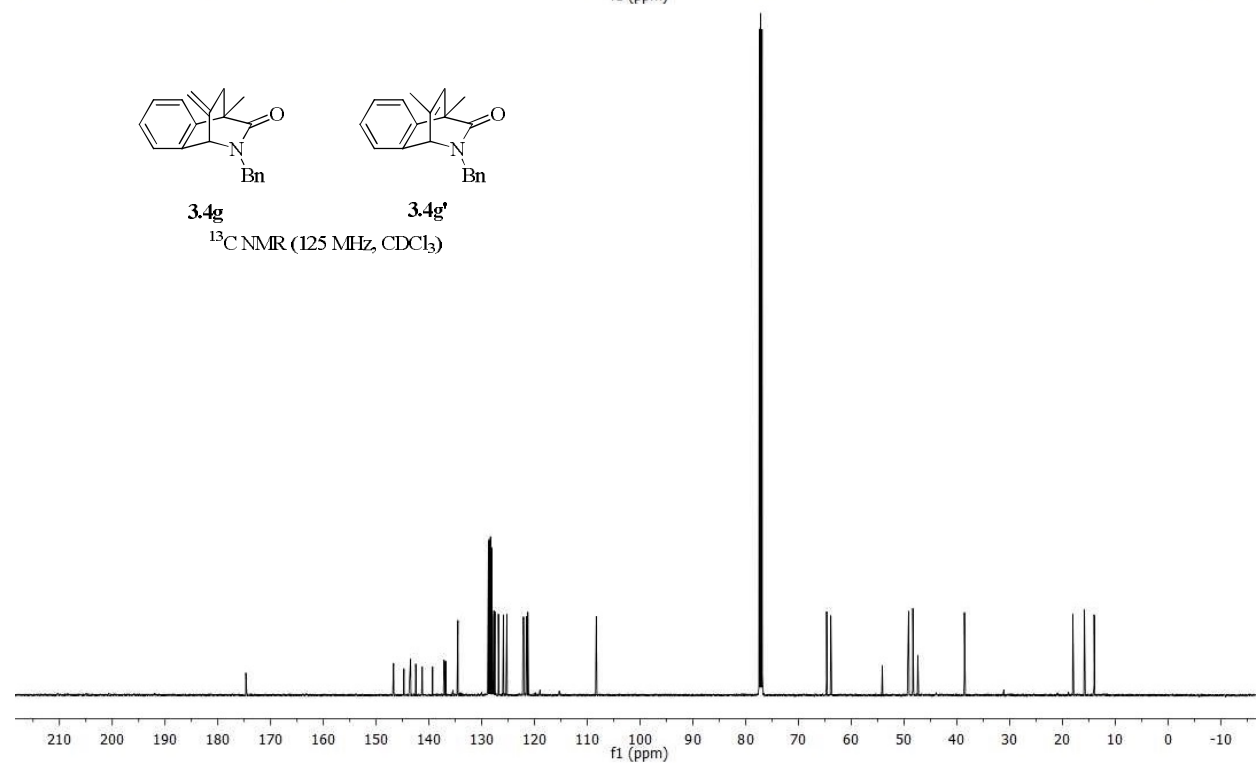
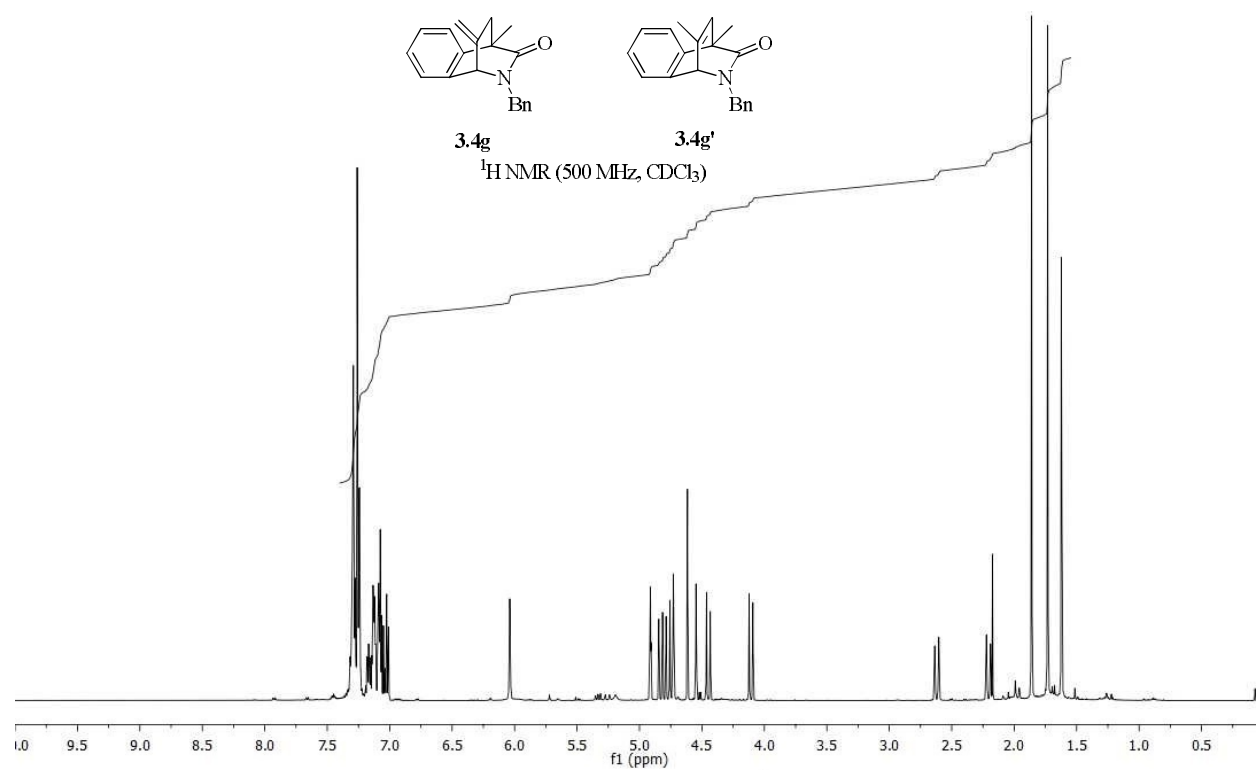


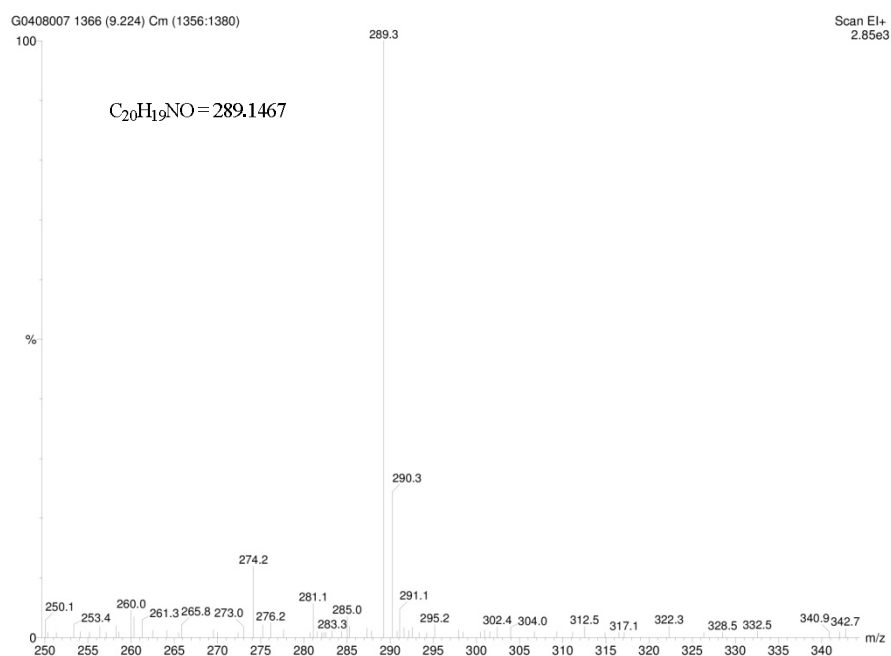
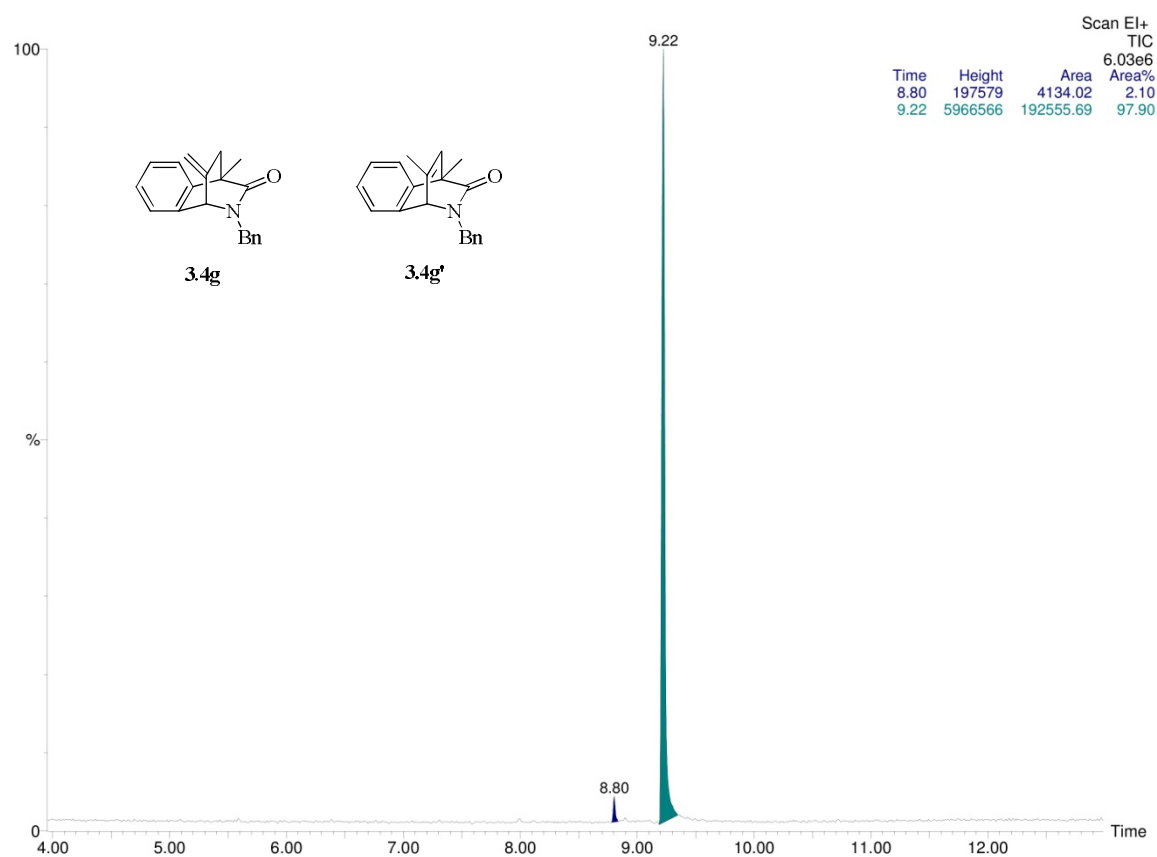


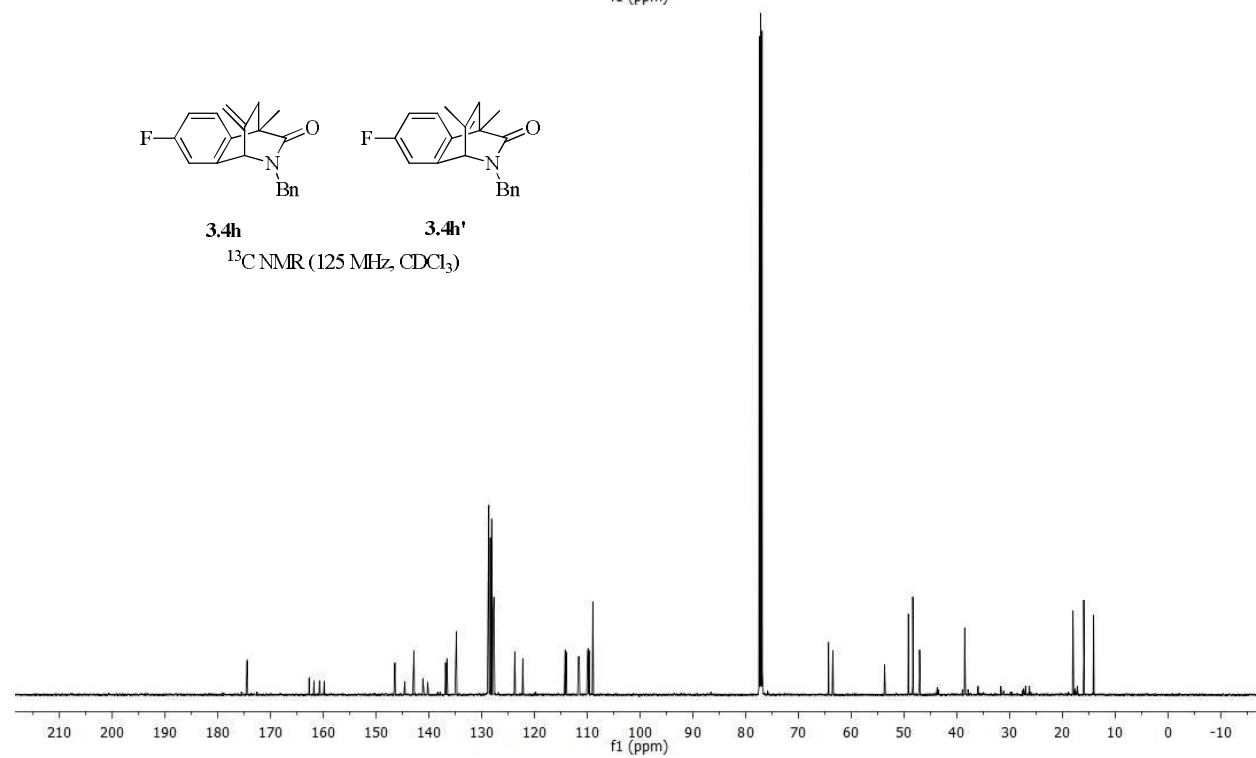
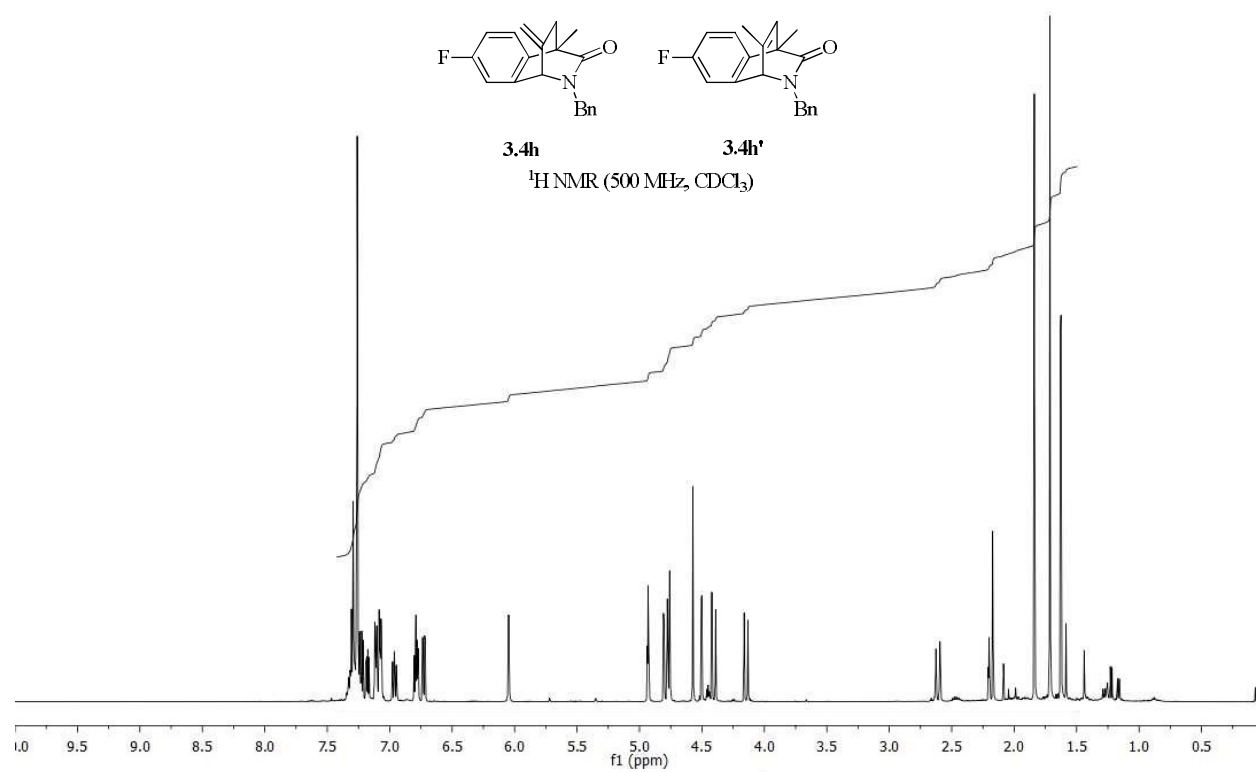


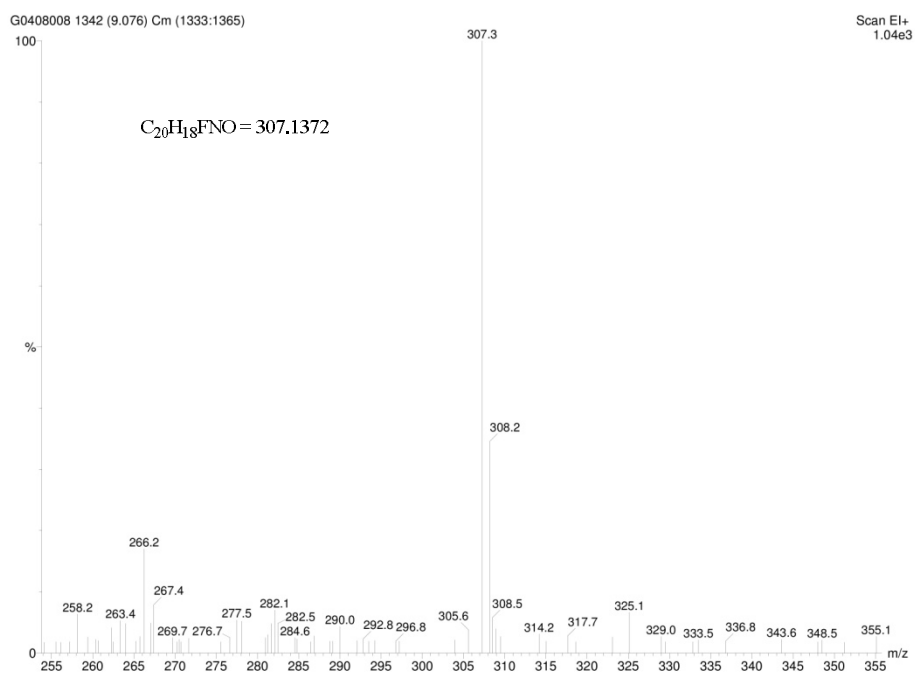
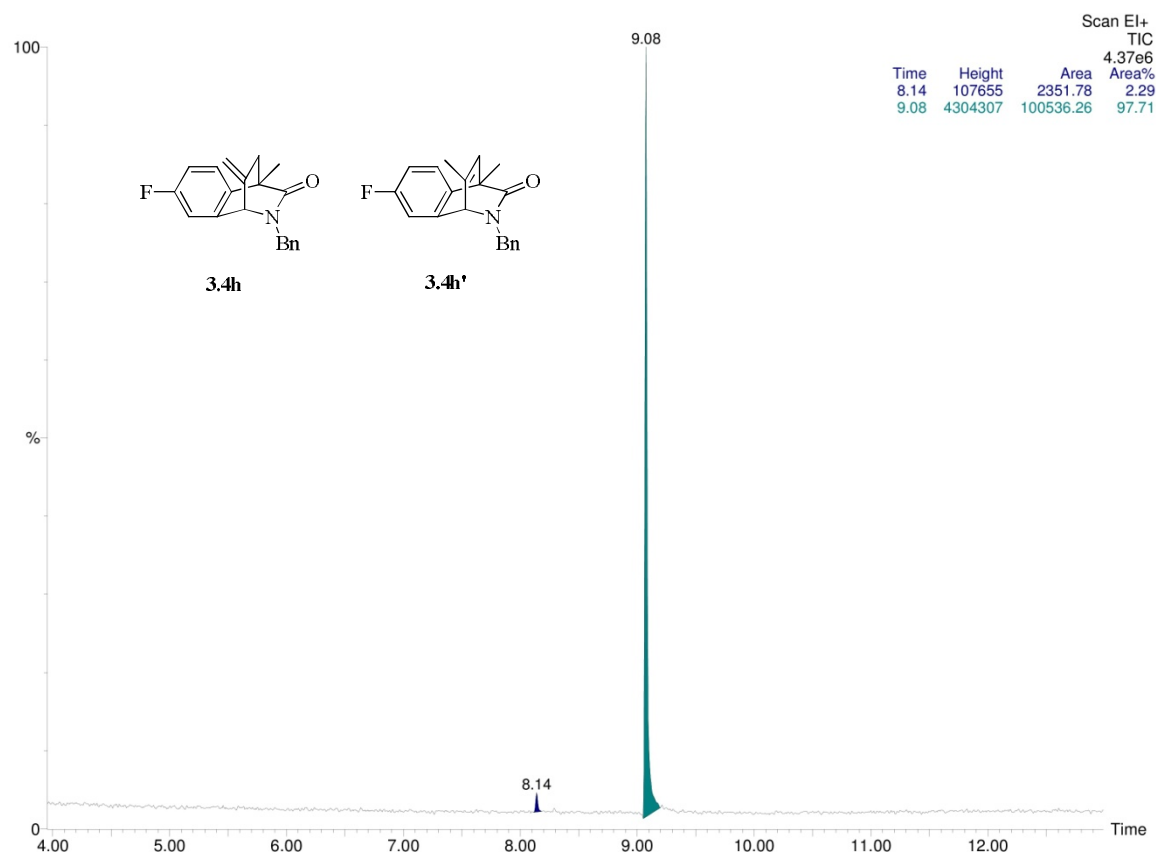


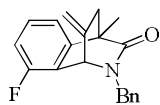






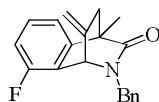
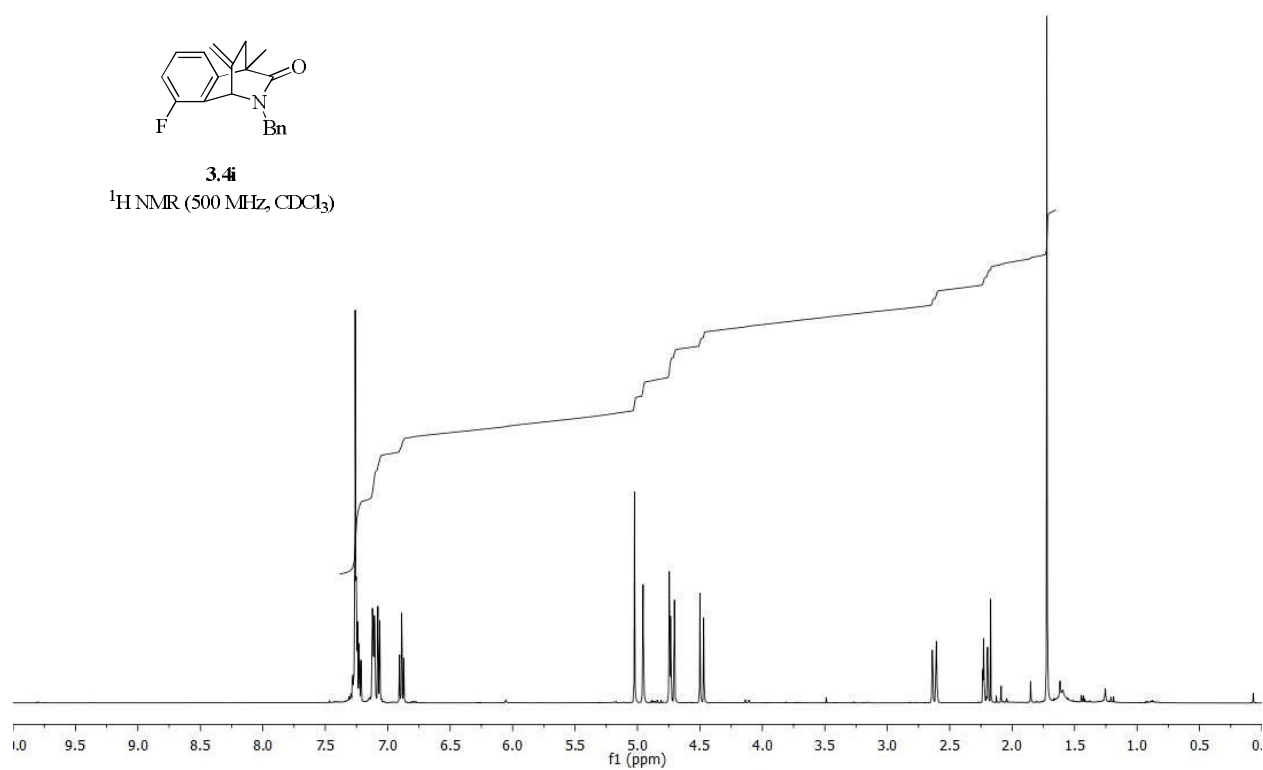






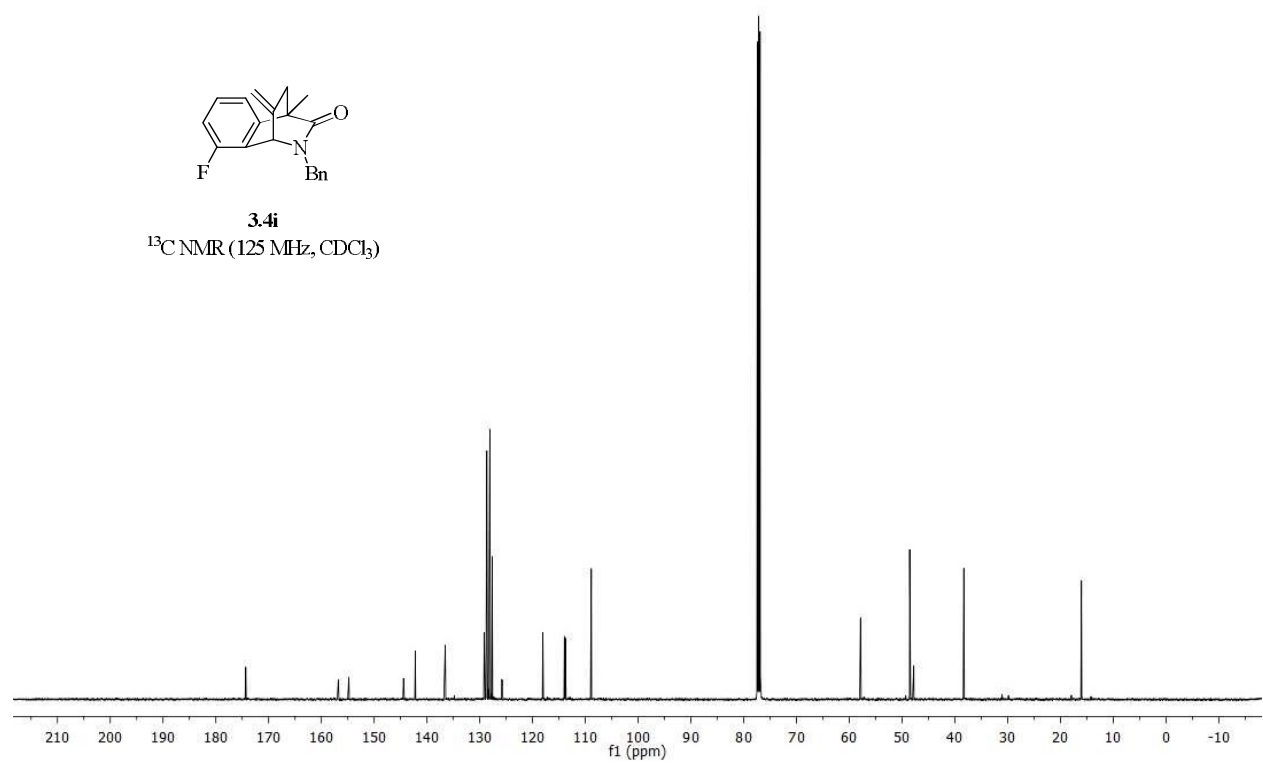
**3.4i**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

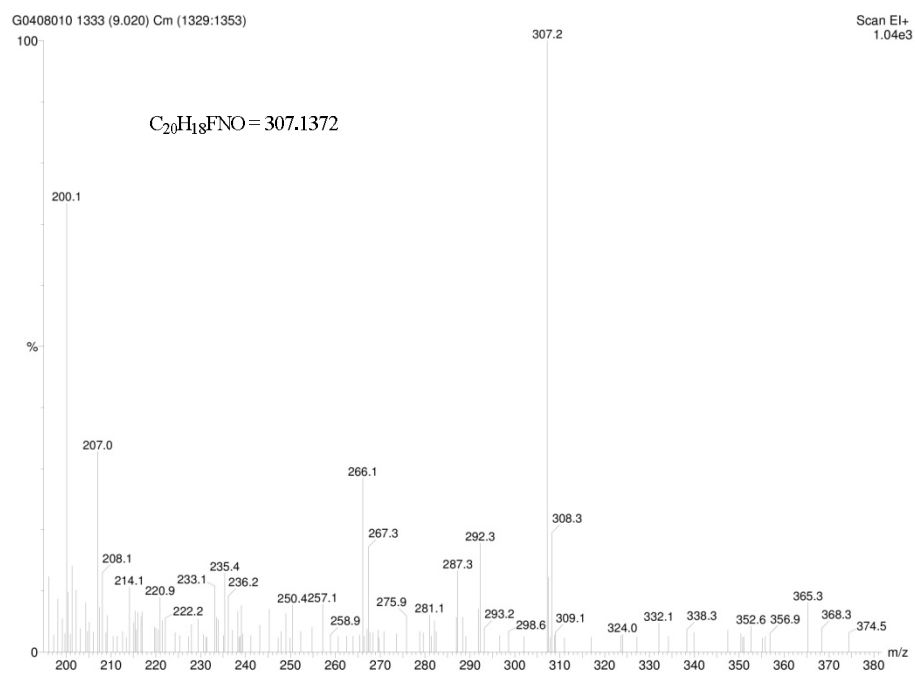
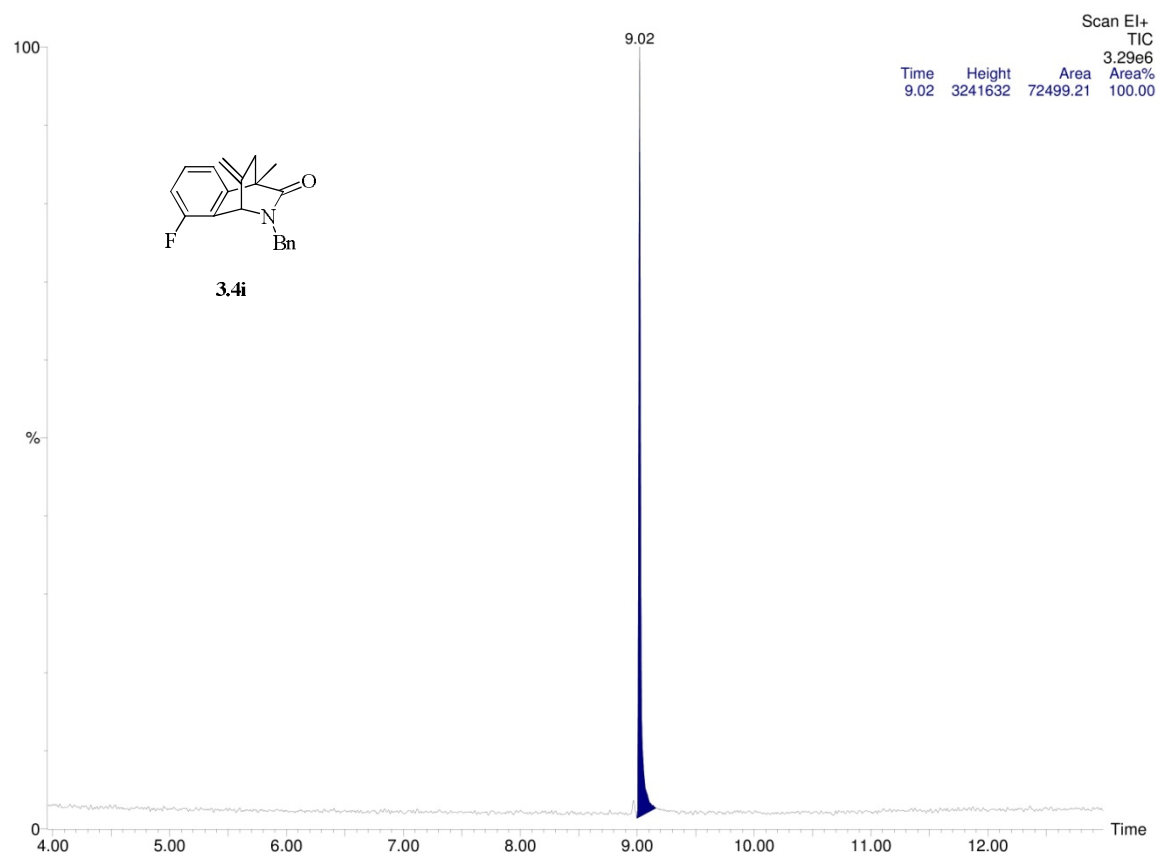


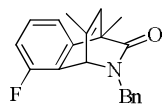
**3.4i**

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )



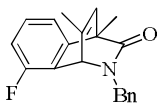
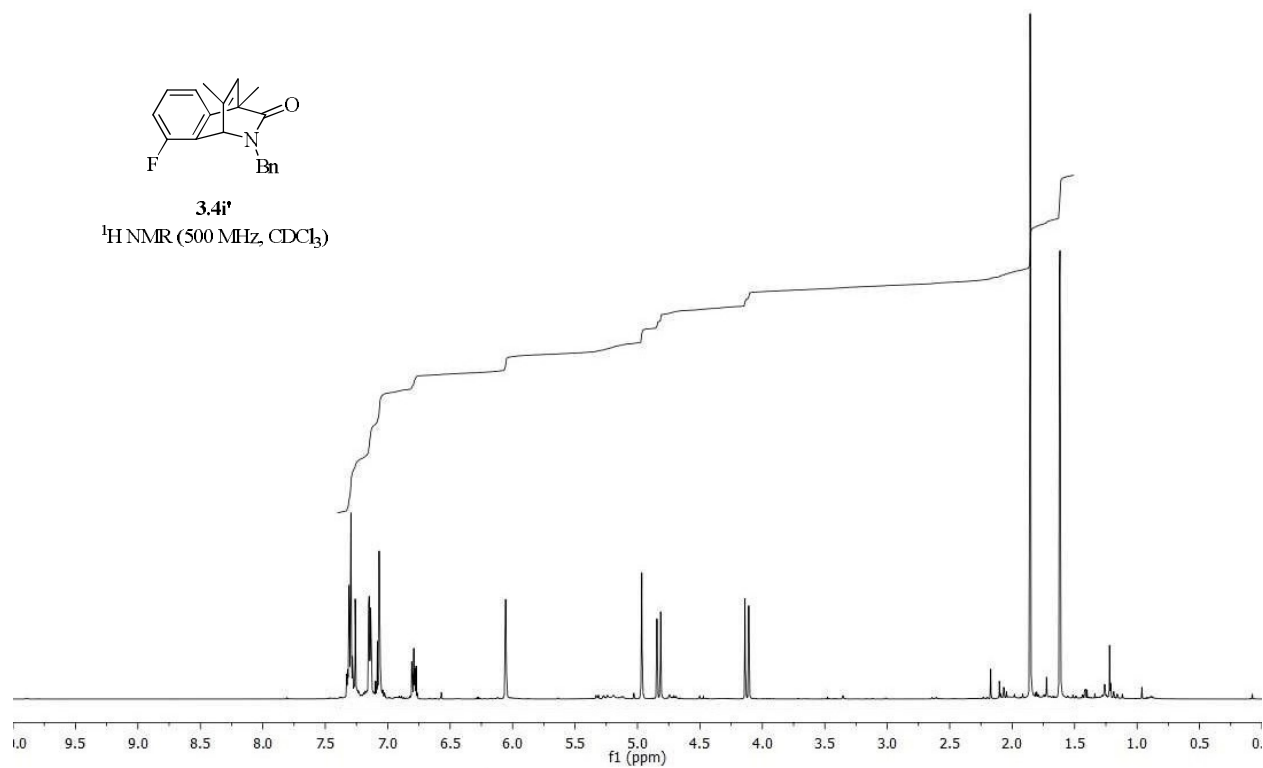






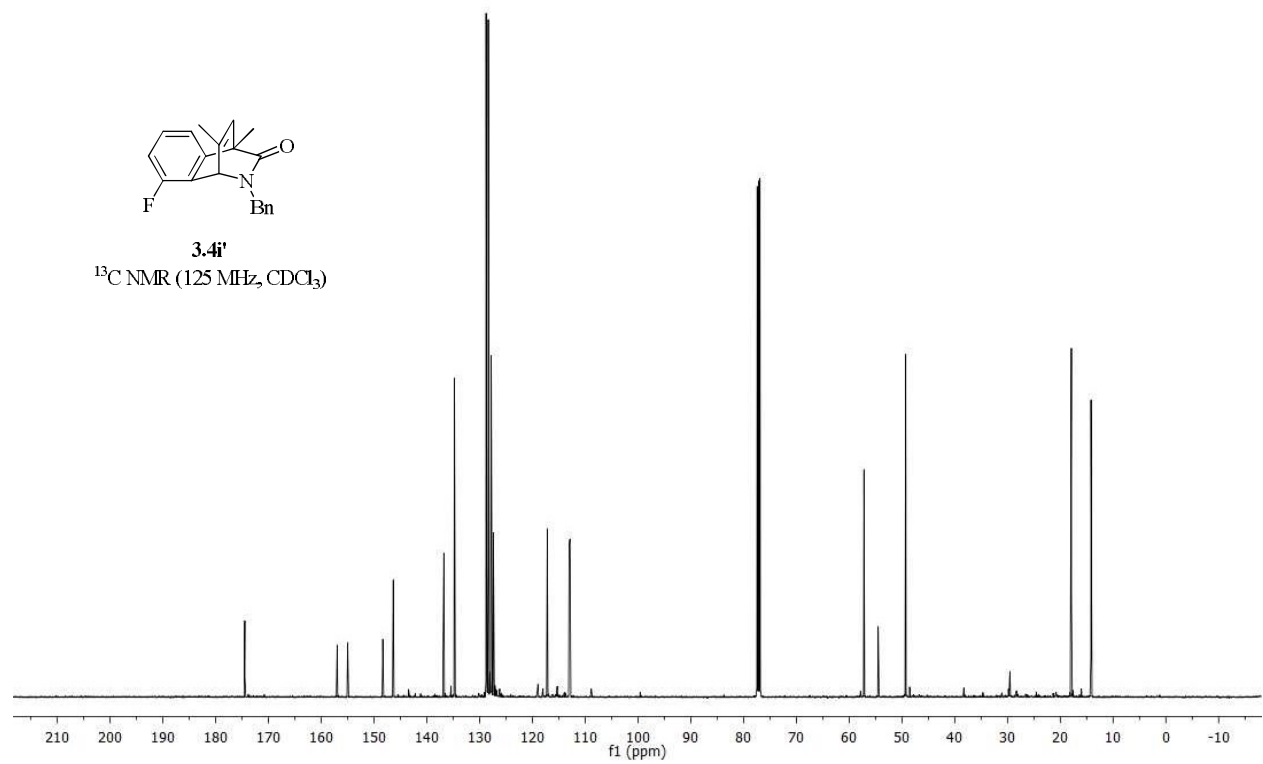
**3.4i'**

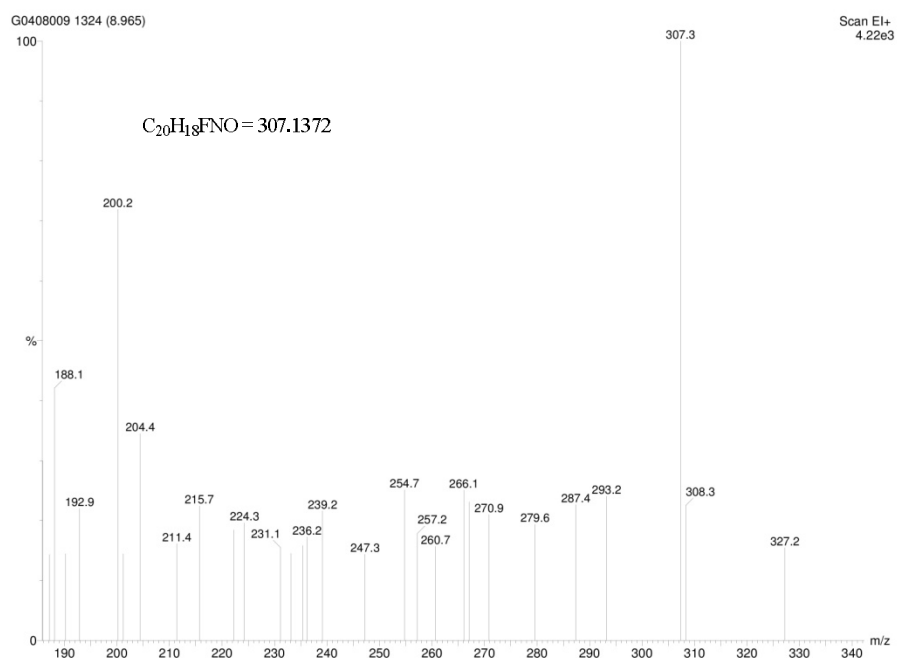
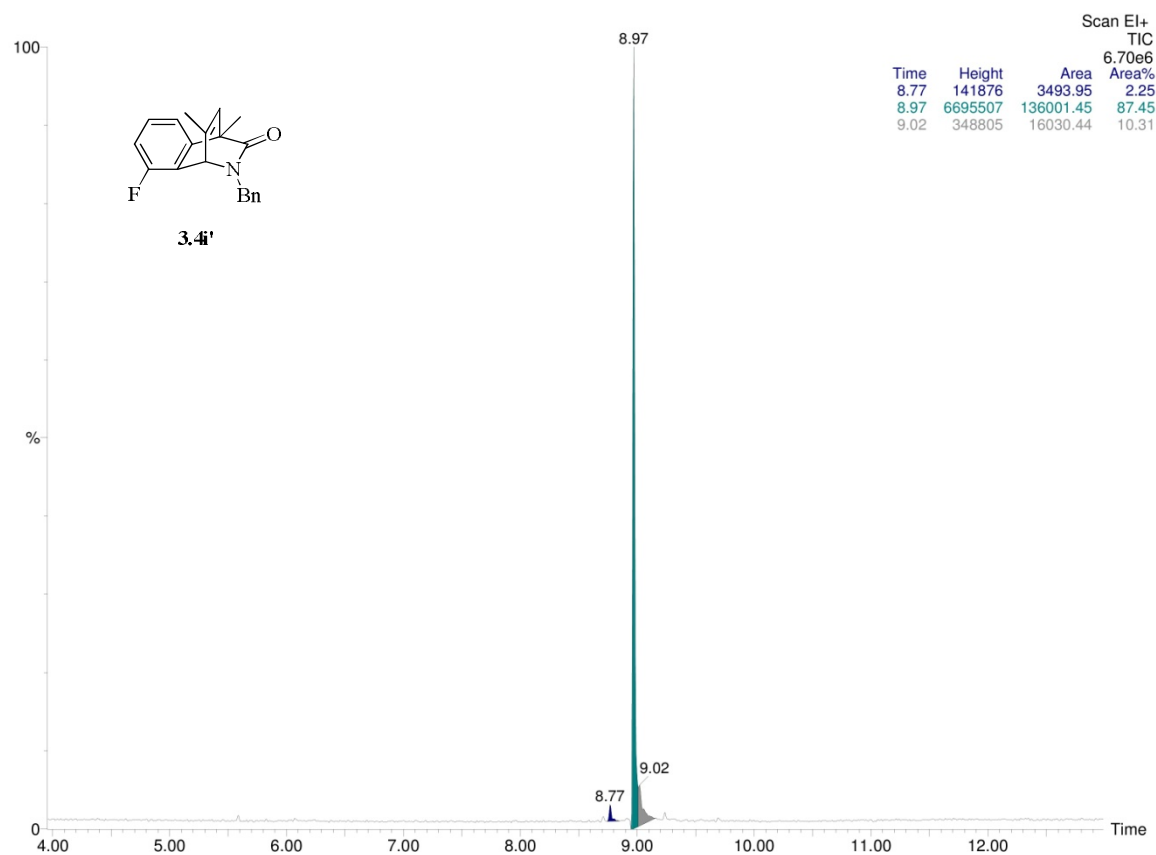
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

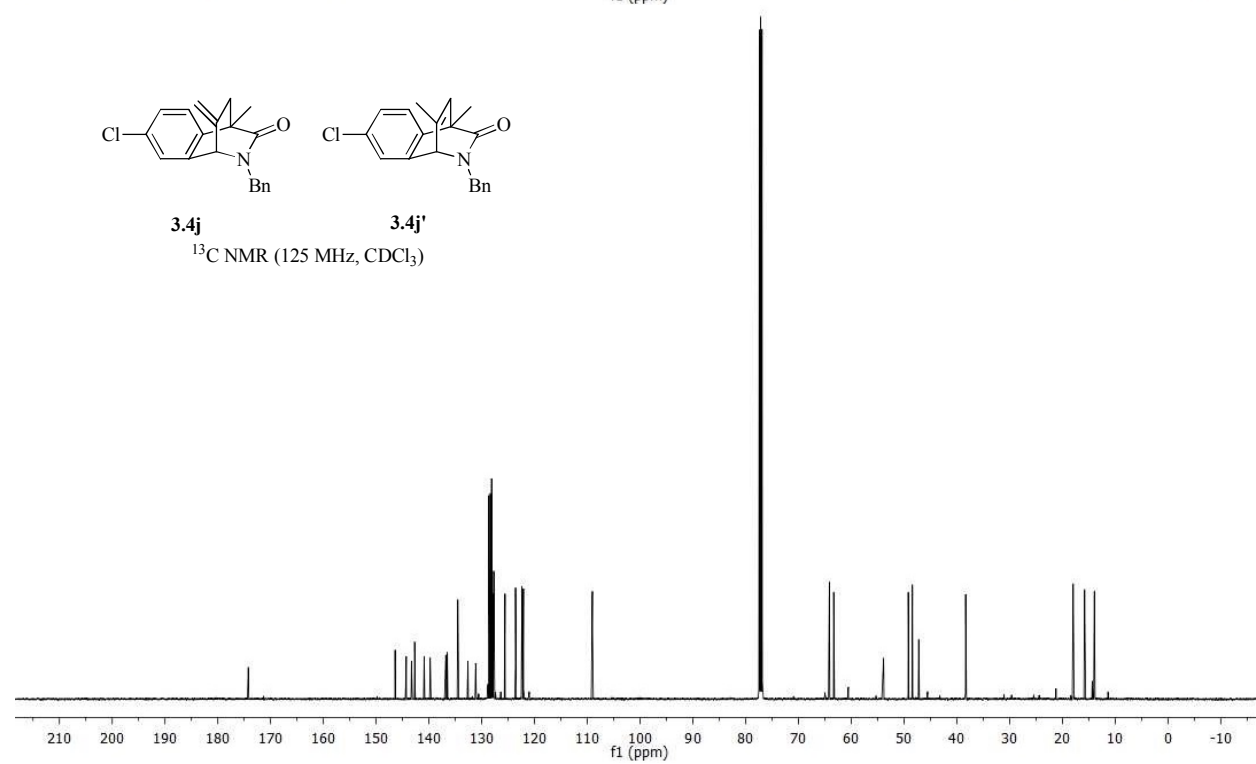
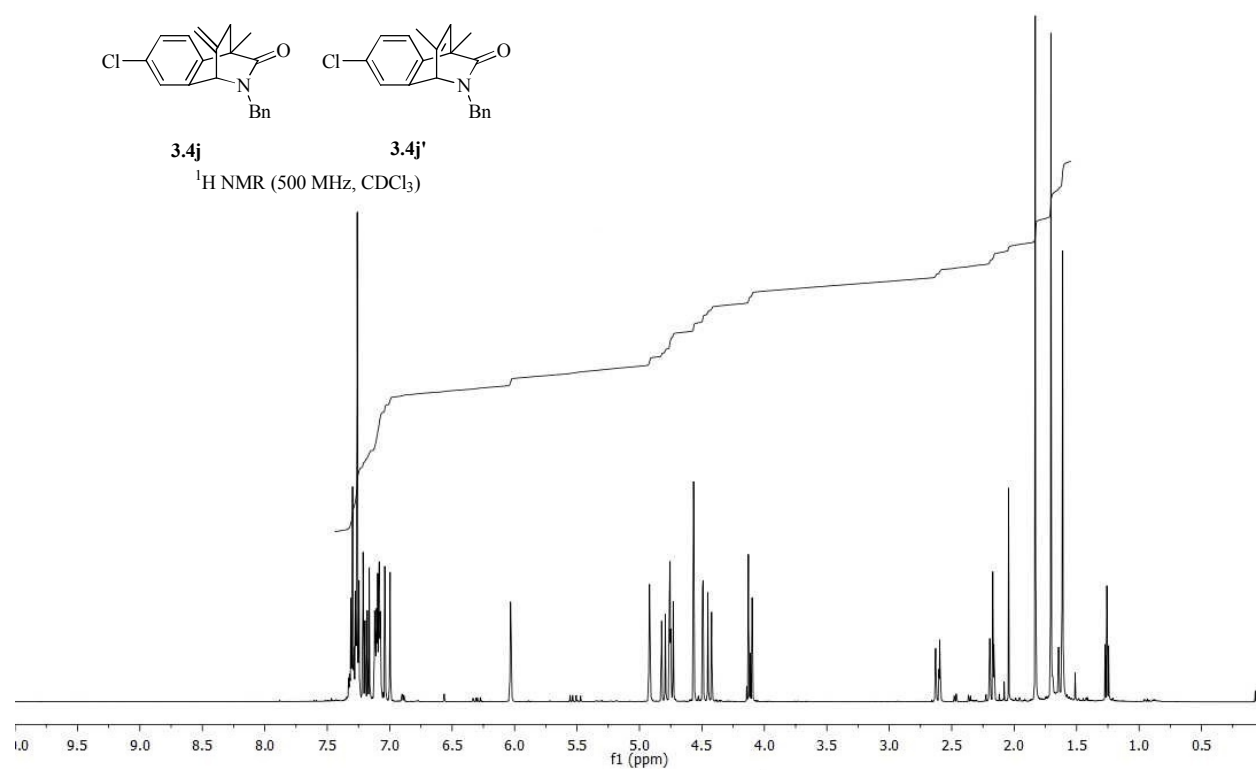


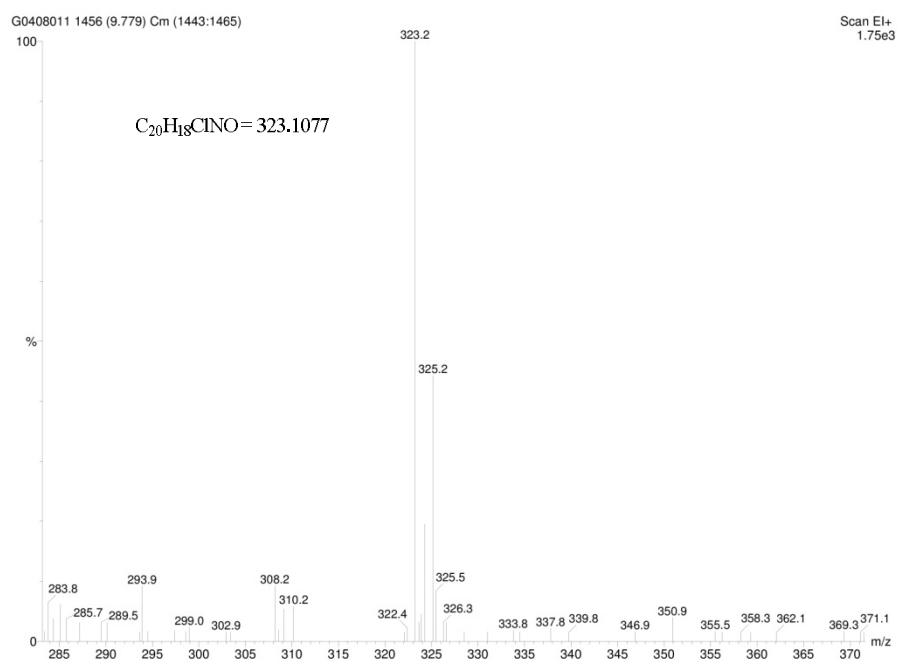
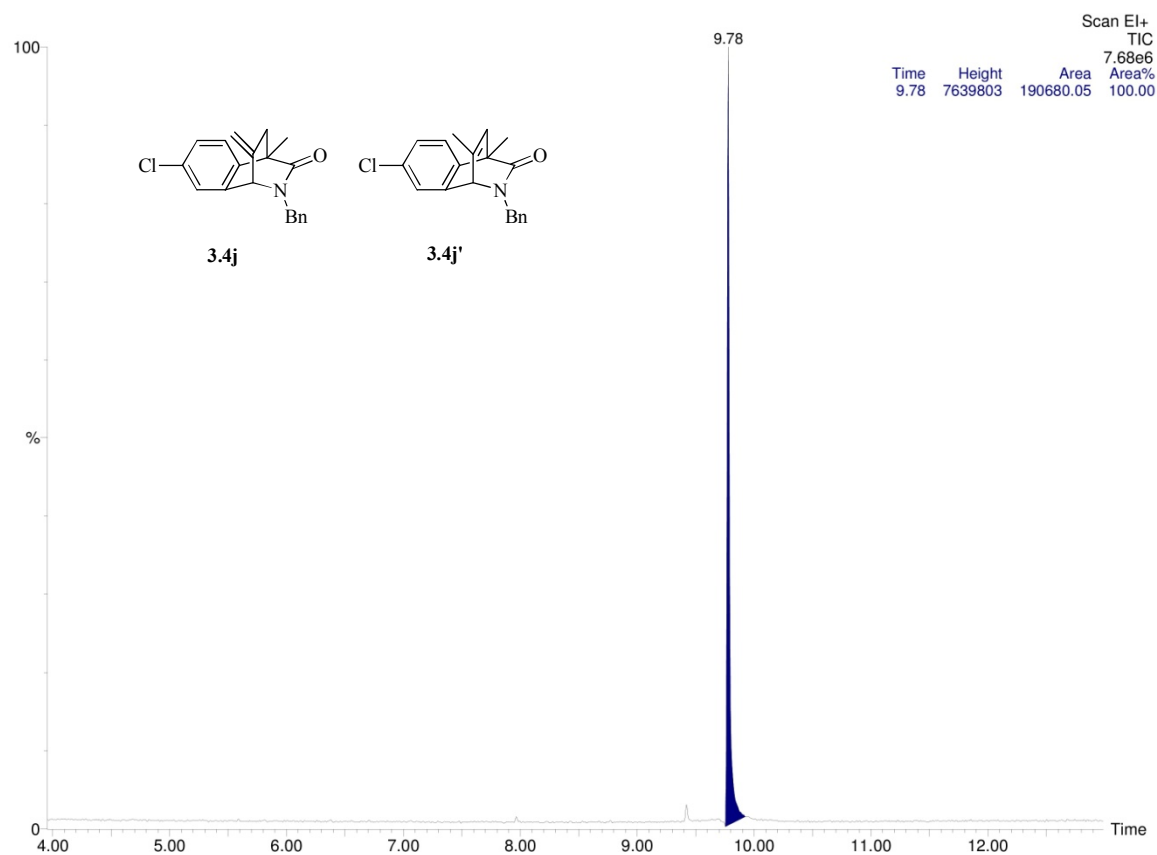
**3.4i'**

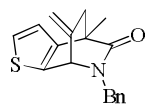
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )





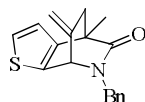
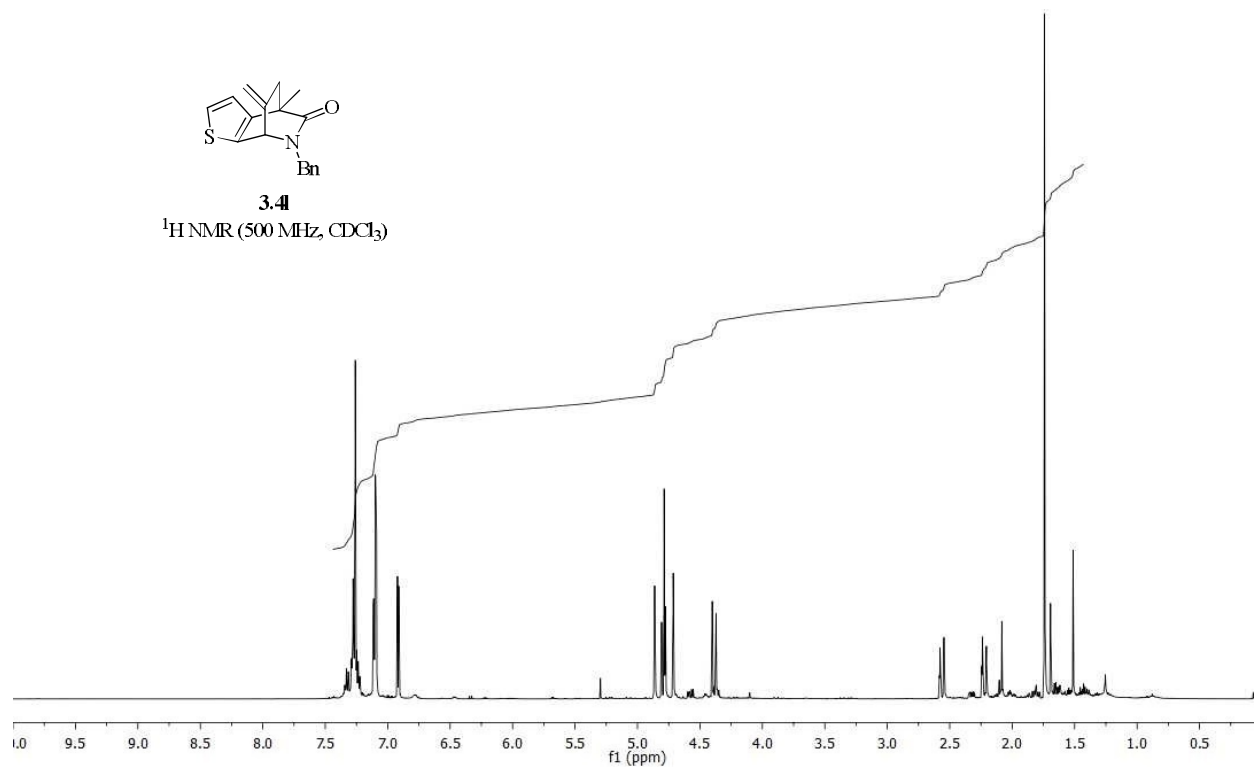






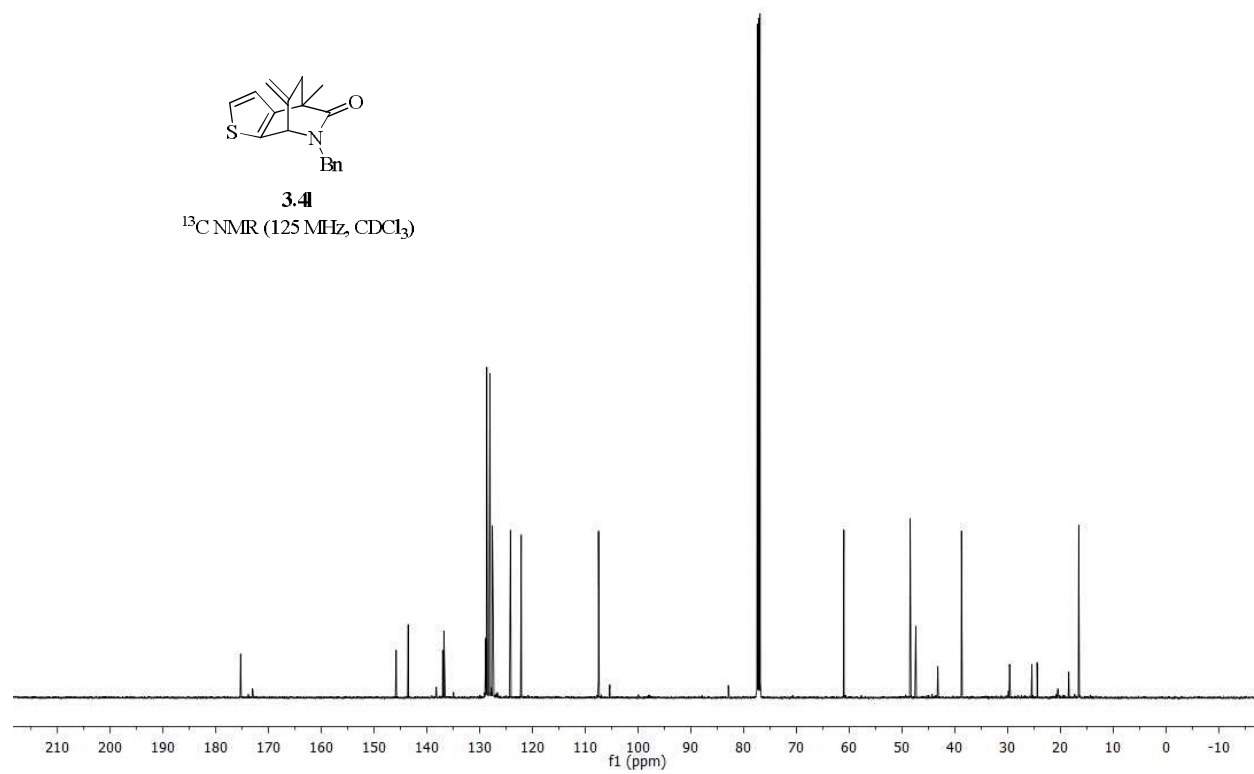
**3.4f**

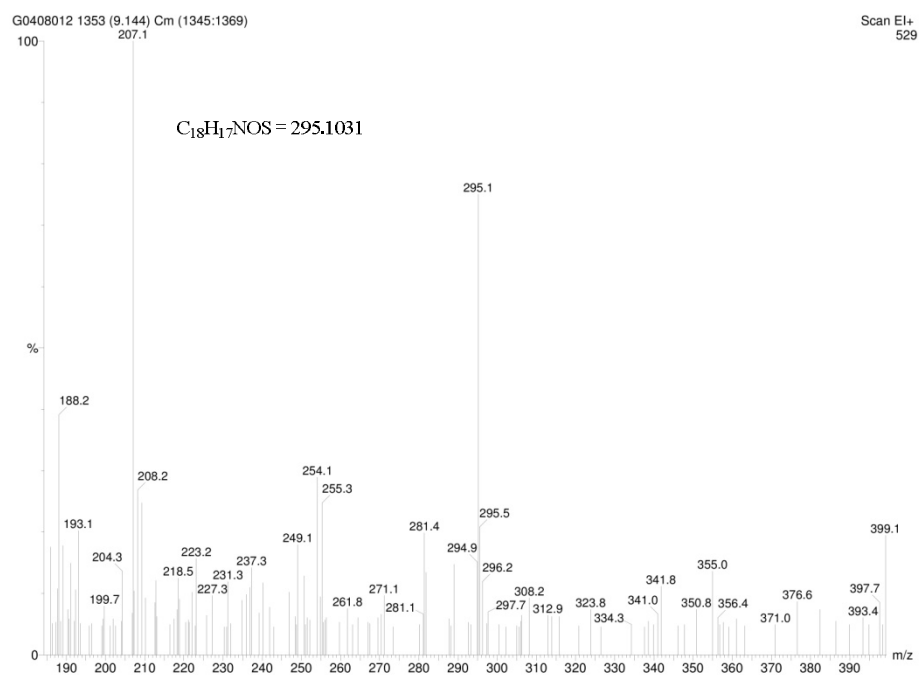
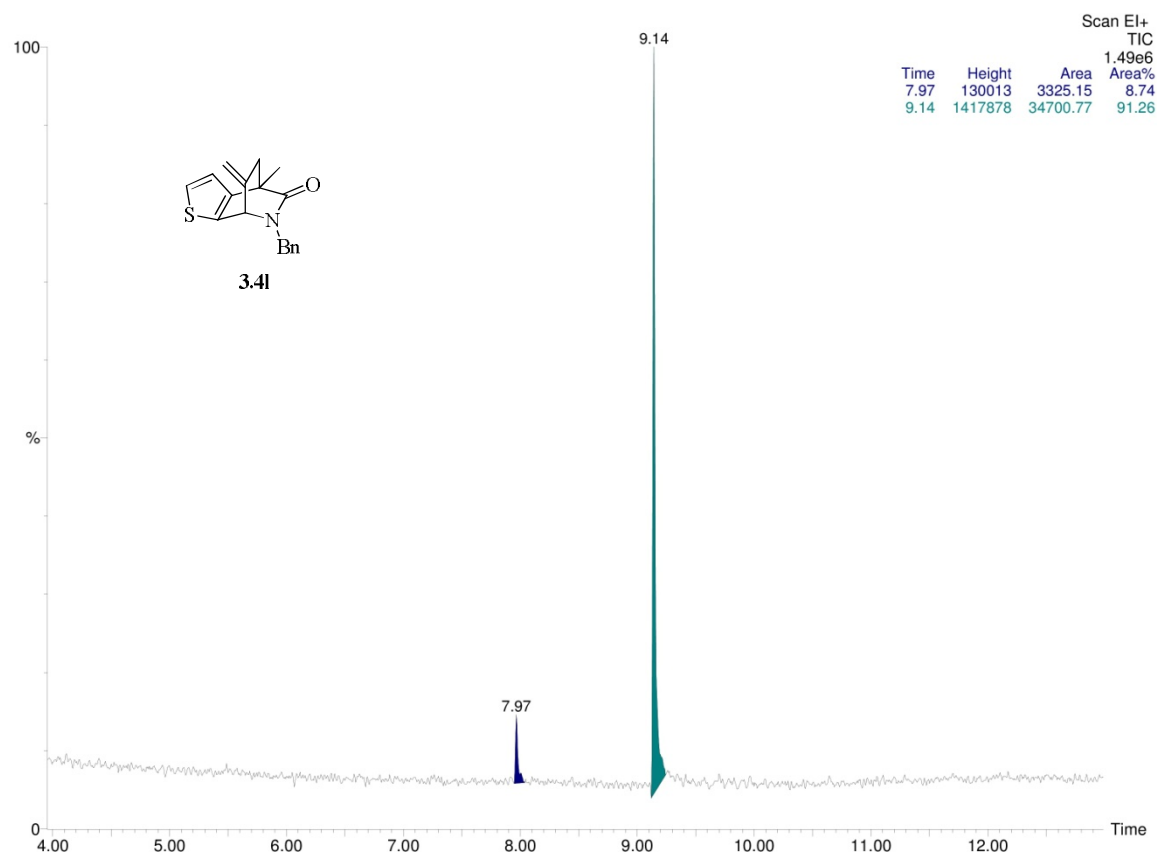
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

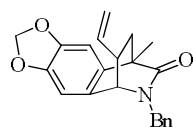


**3.4f**

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)

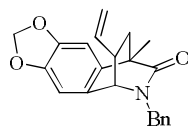
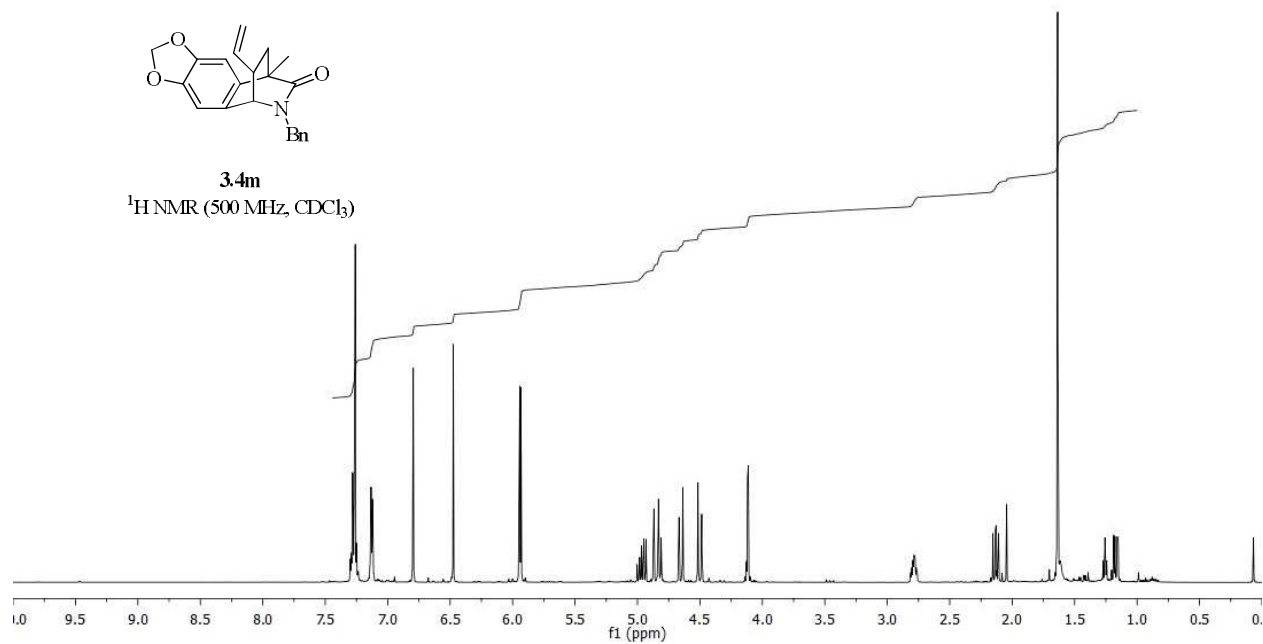






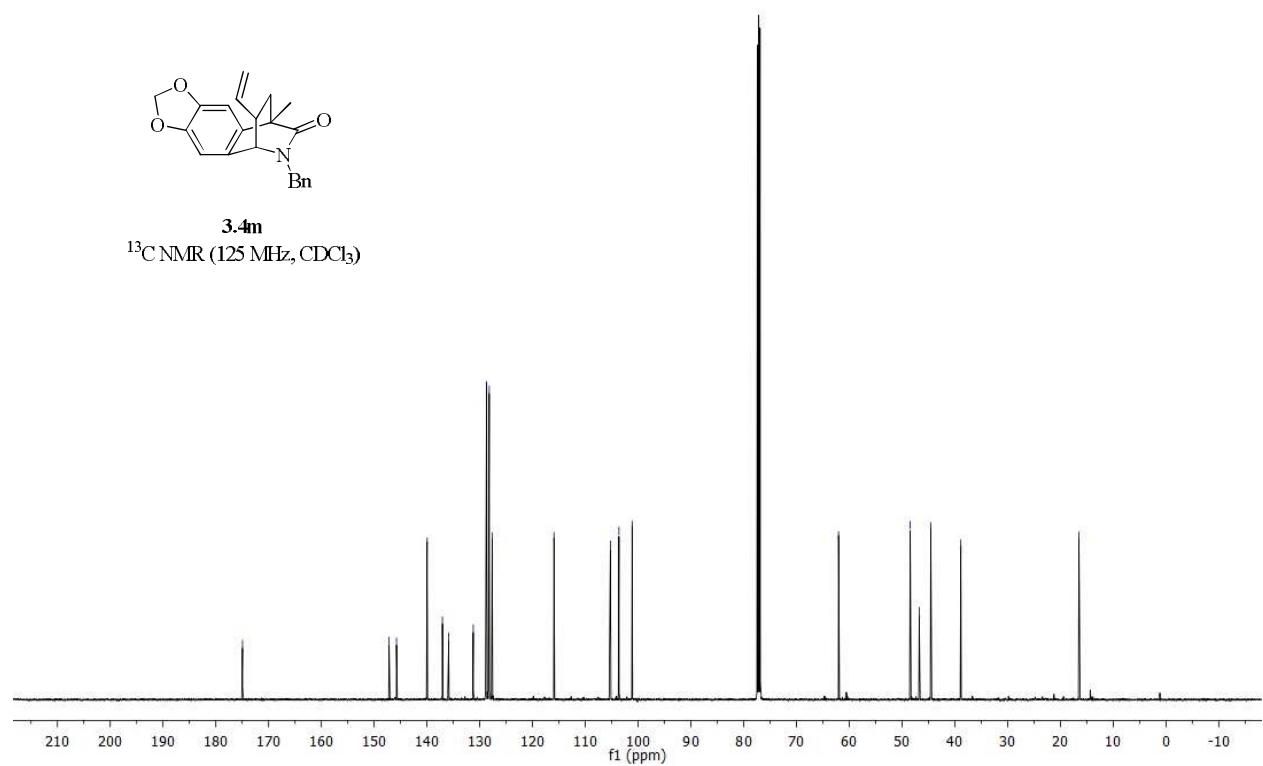
**3.4m**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

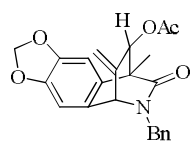


**3.4m**

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )

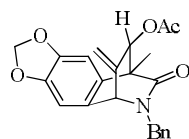
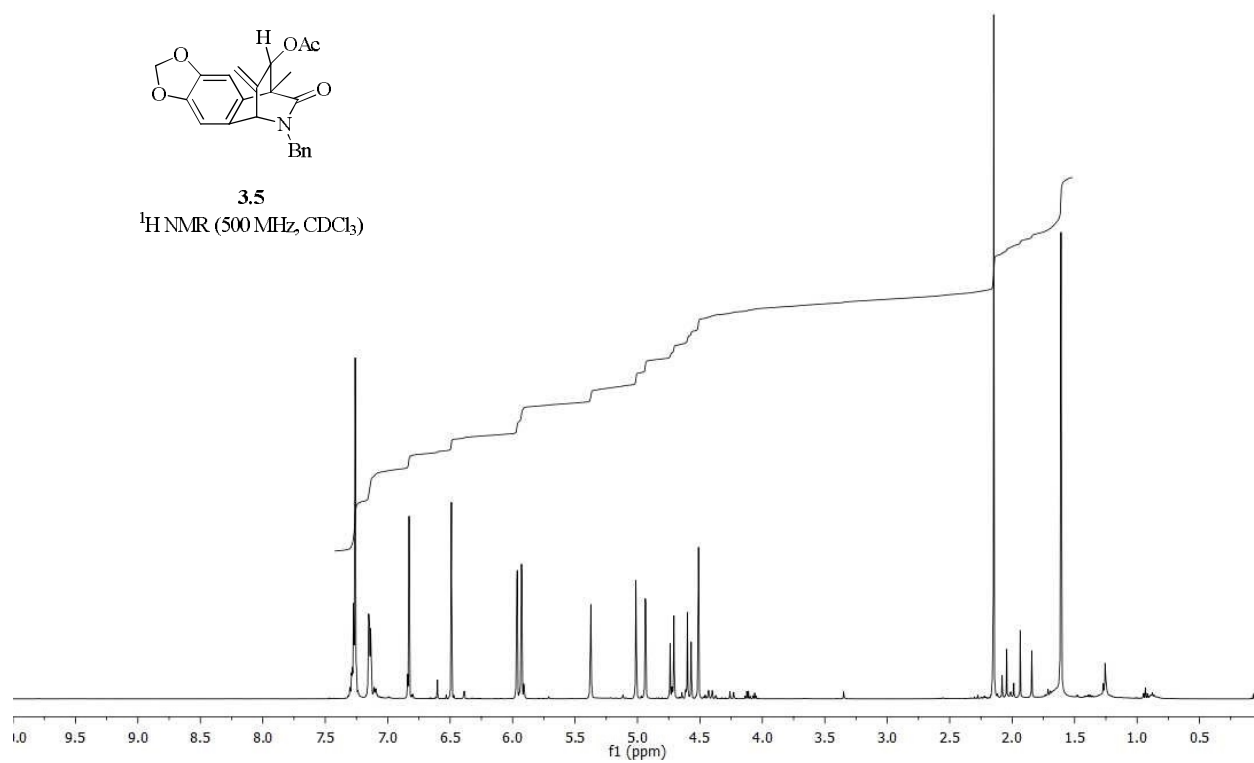






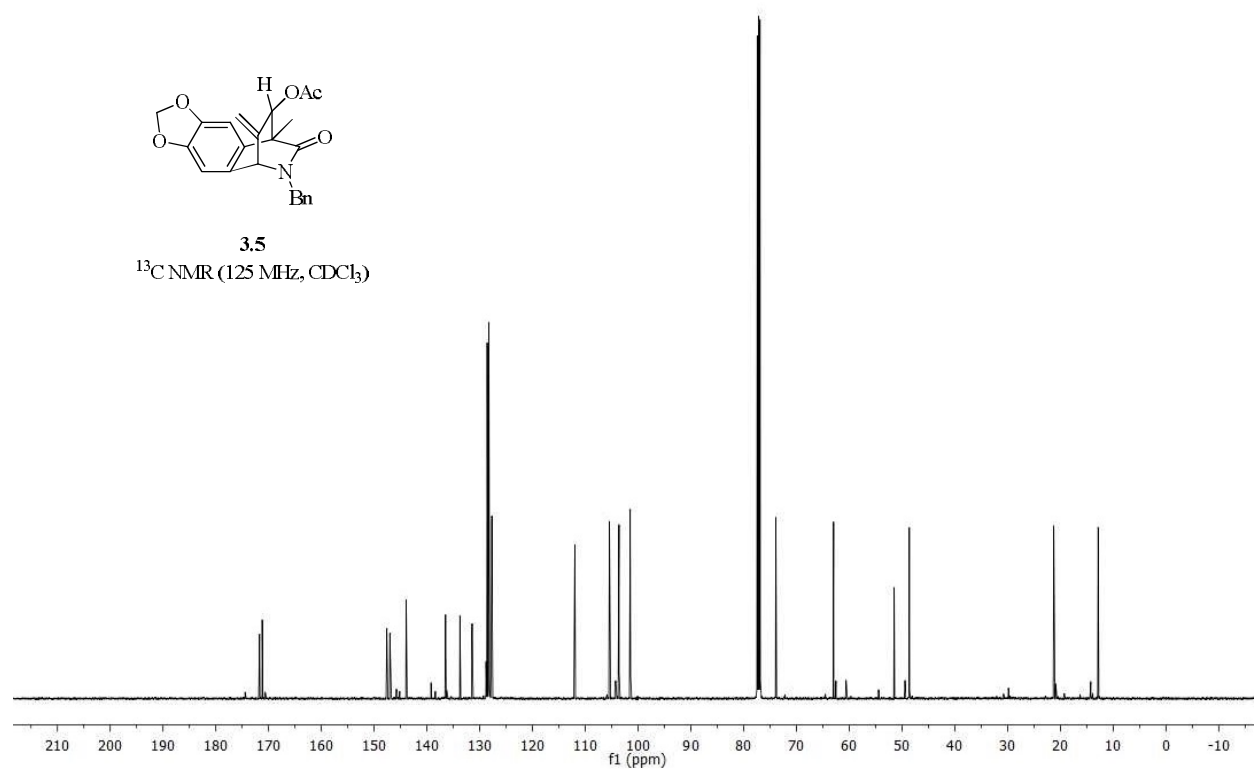
**3.5**

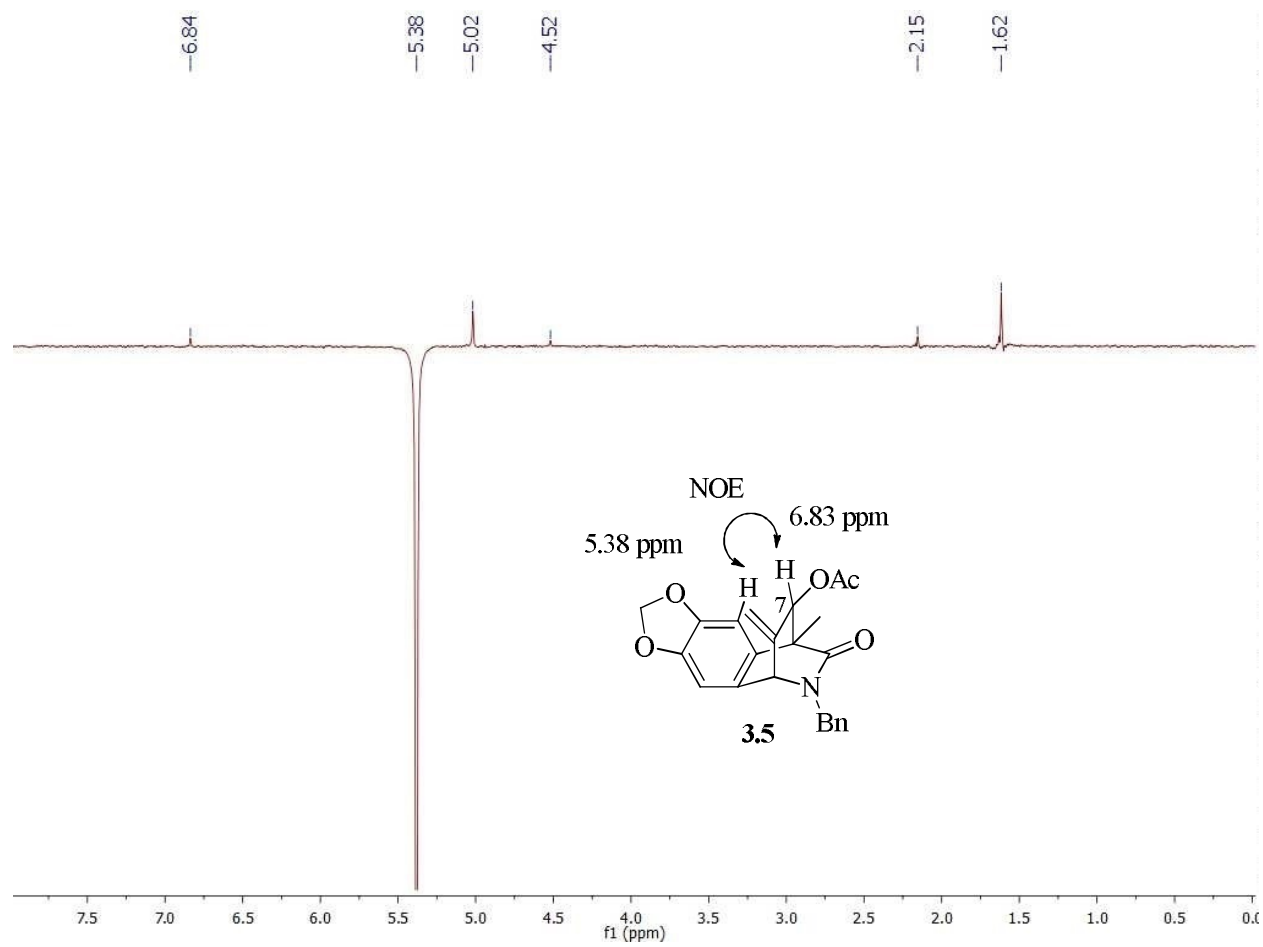
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

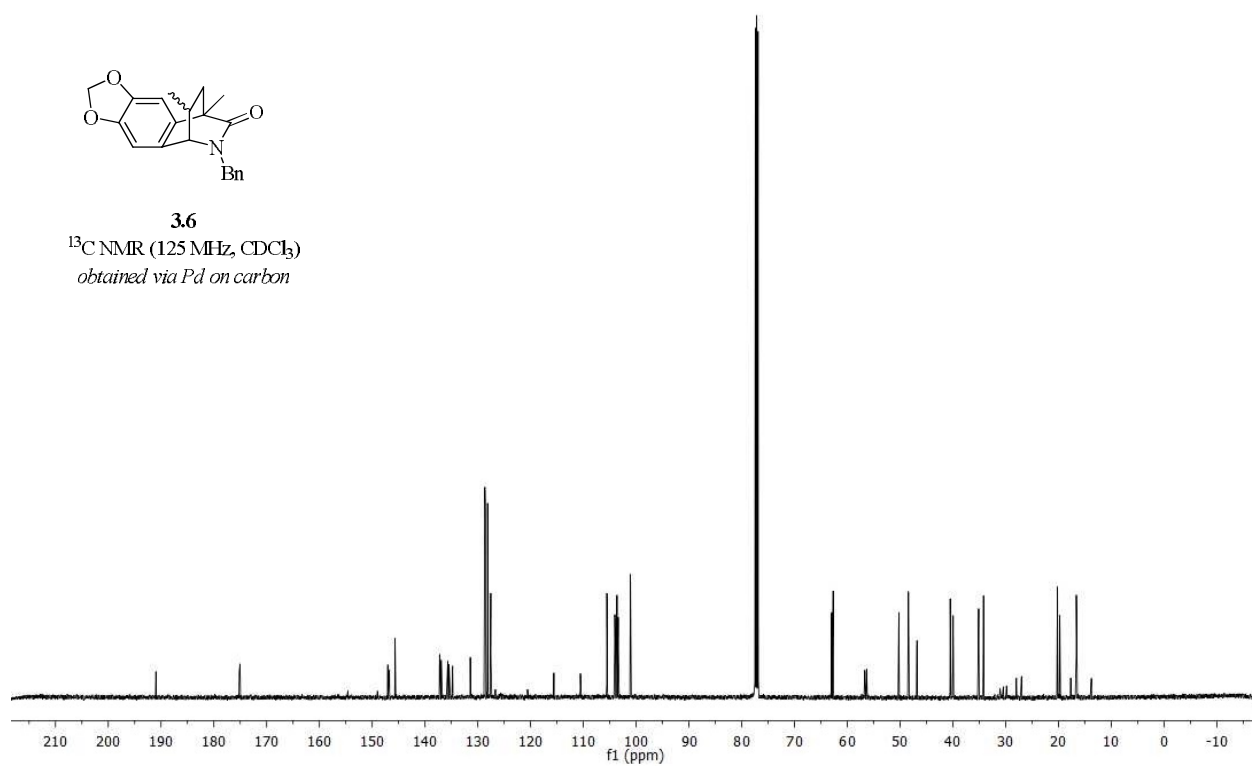
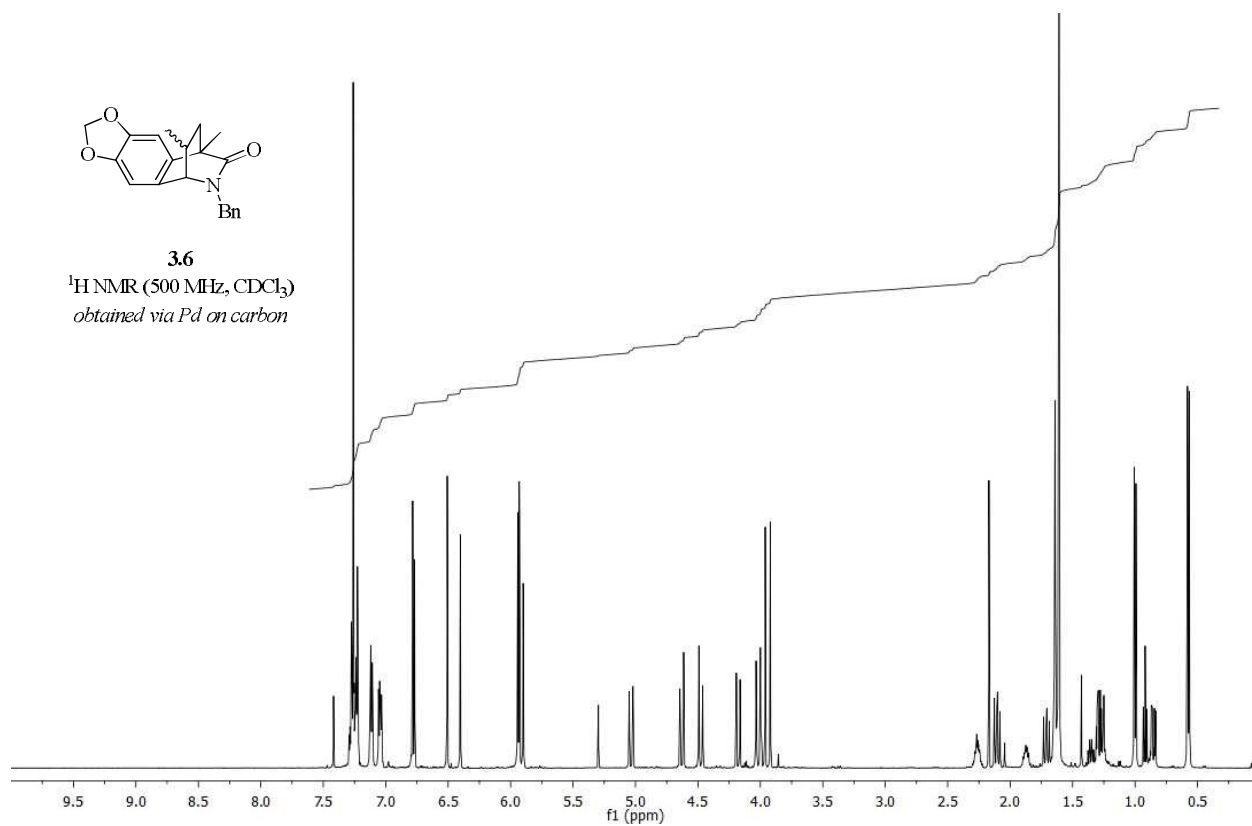


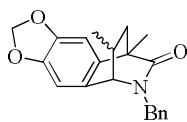
**3.5**

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )



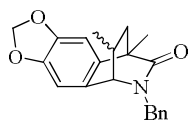
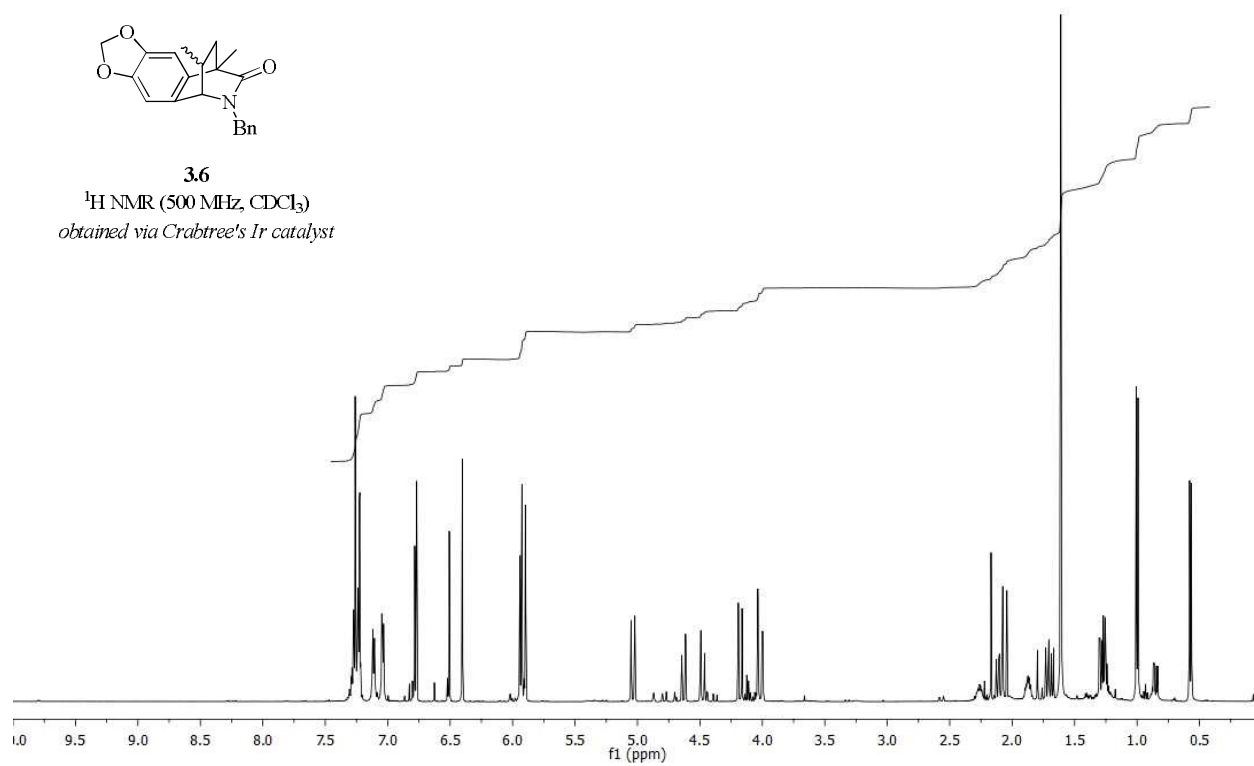






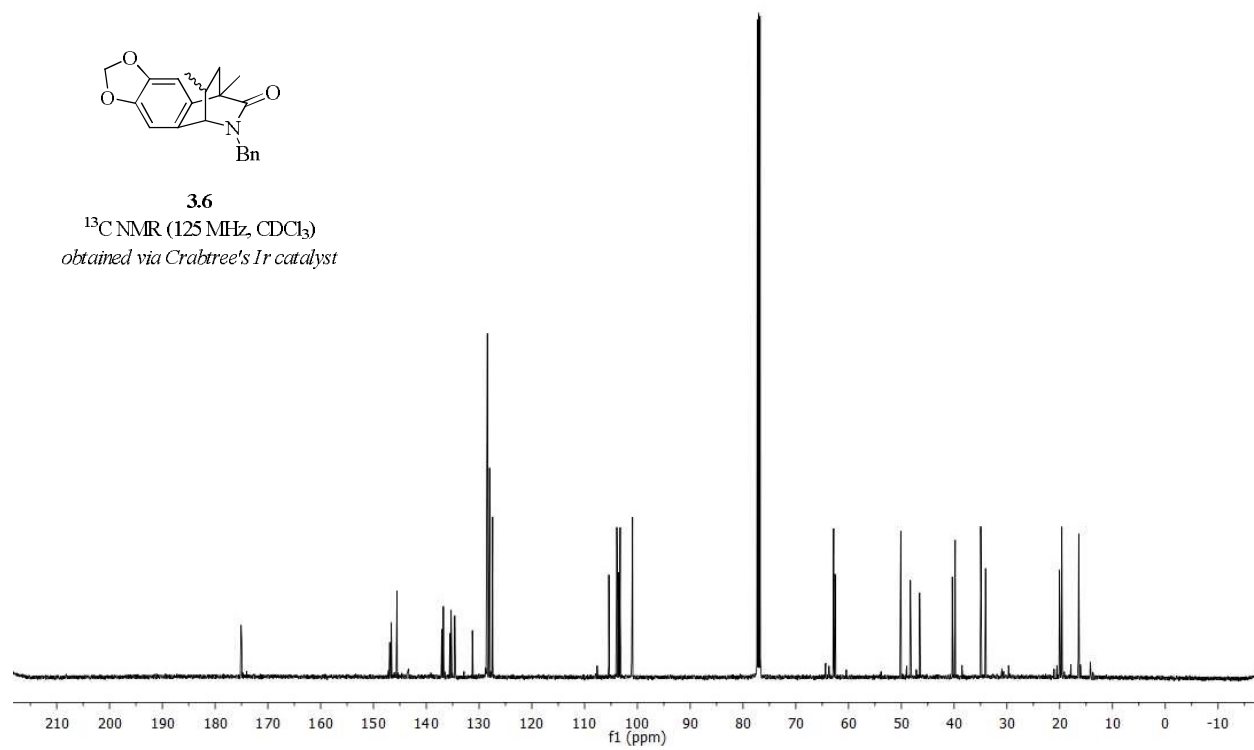
**3.6**

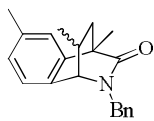
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  
obtained via Crabtree's Ir catalyst



**3.6**

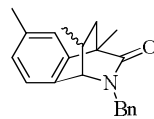
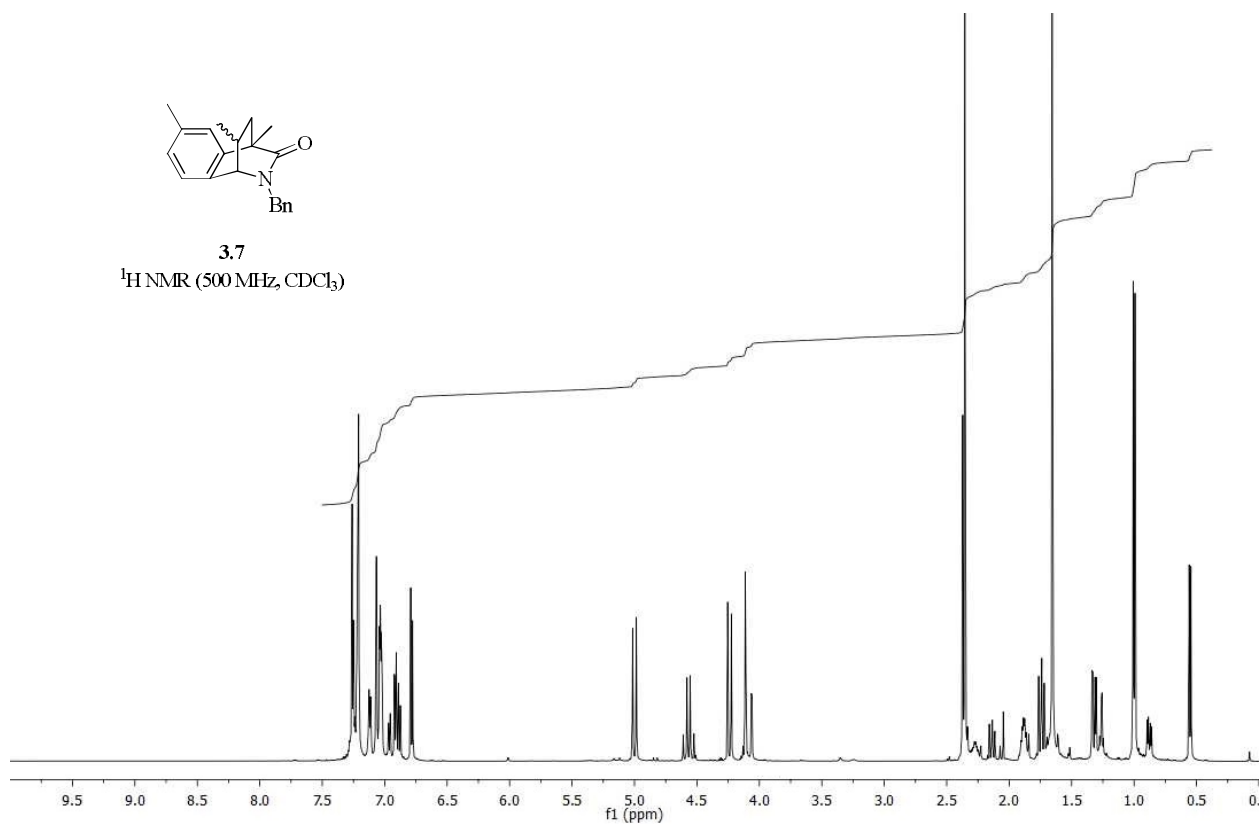
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  
obtained via Crabtree's Ir catalyst





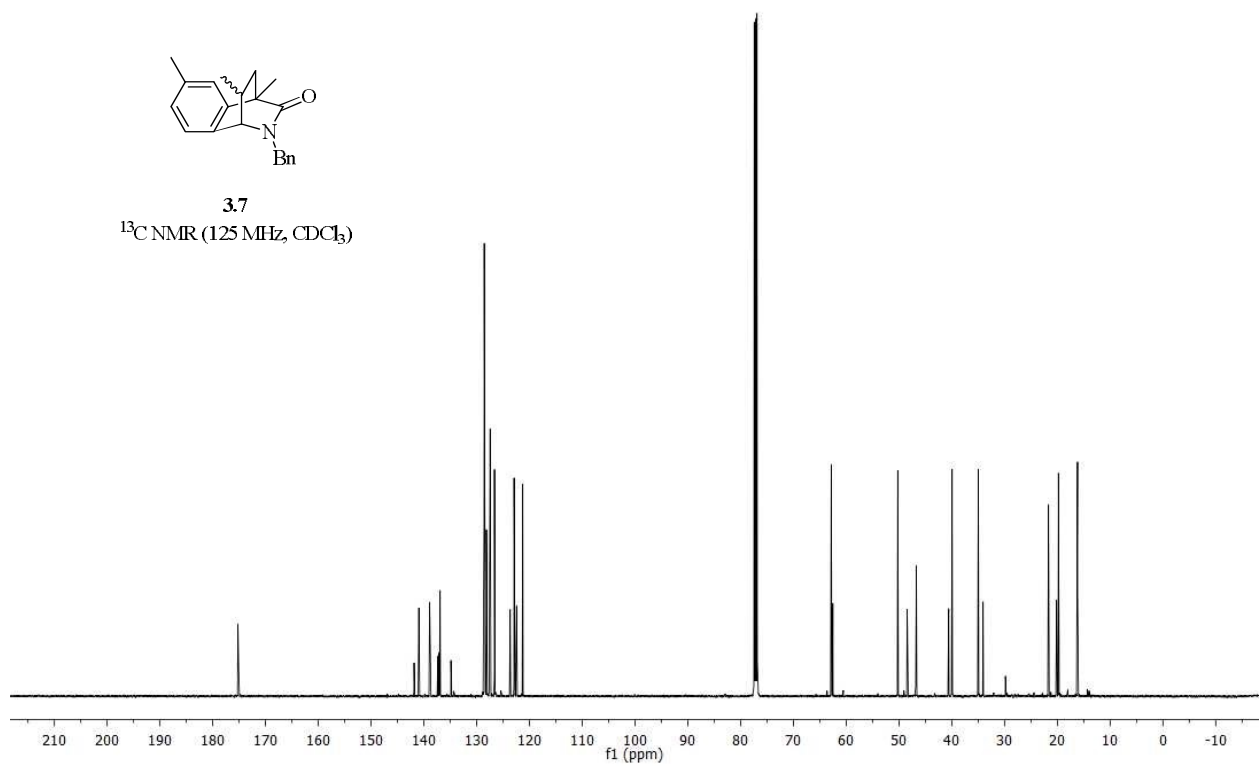
**3.7**

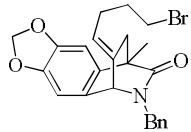
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



**3.7**

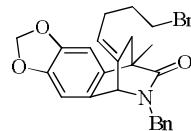
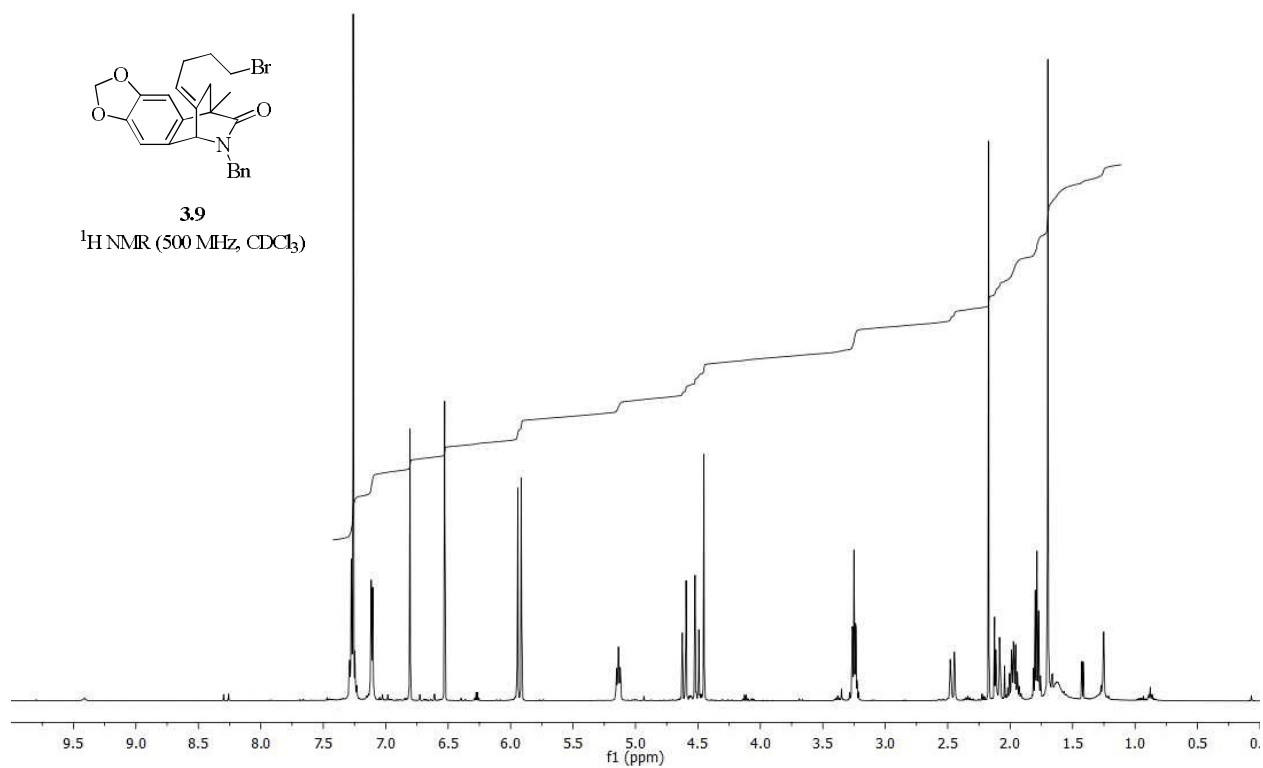
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )





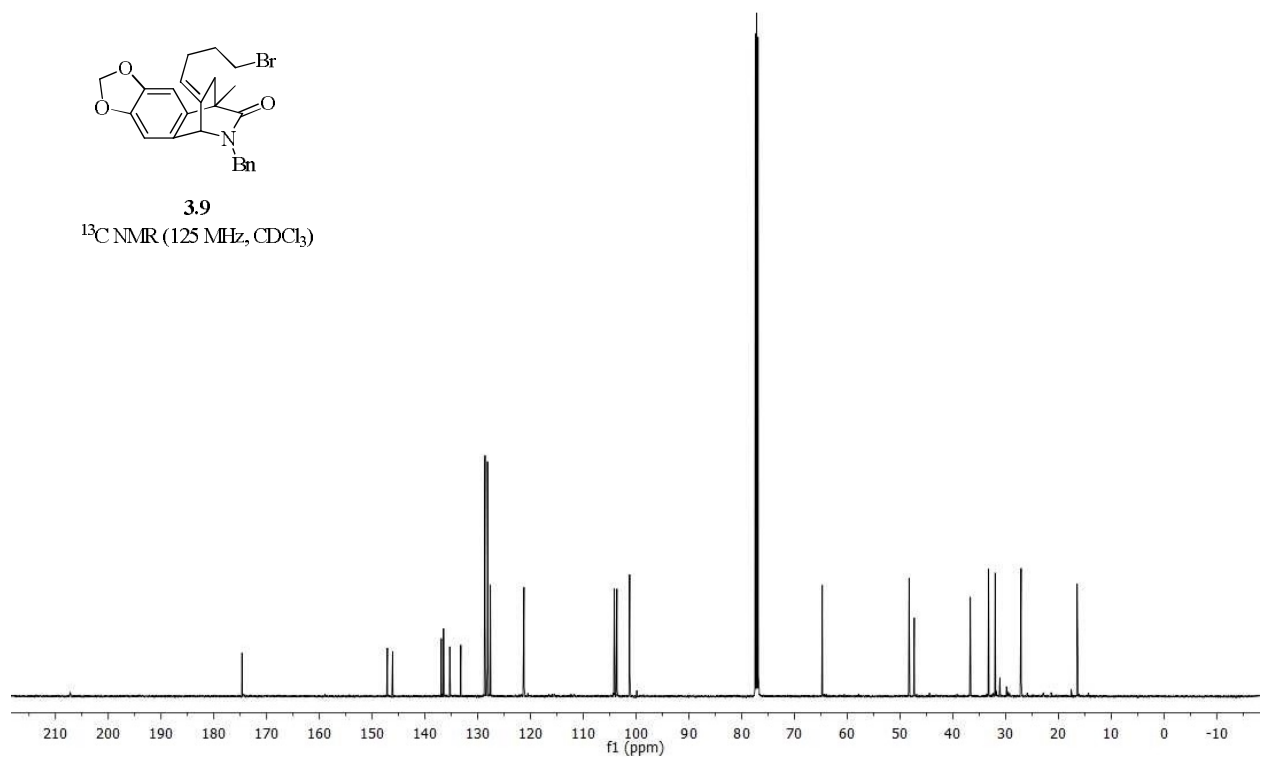
**3.9**

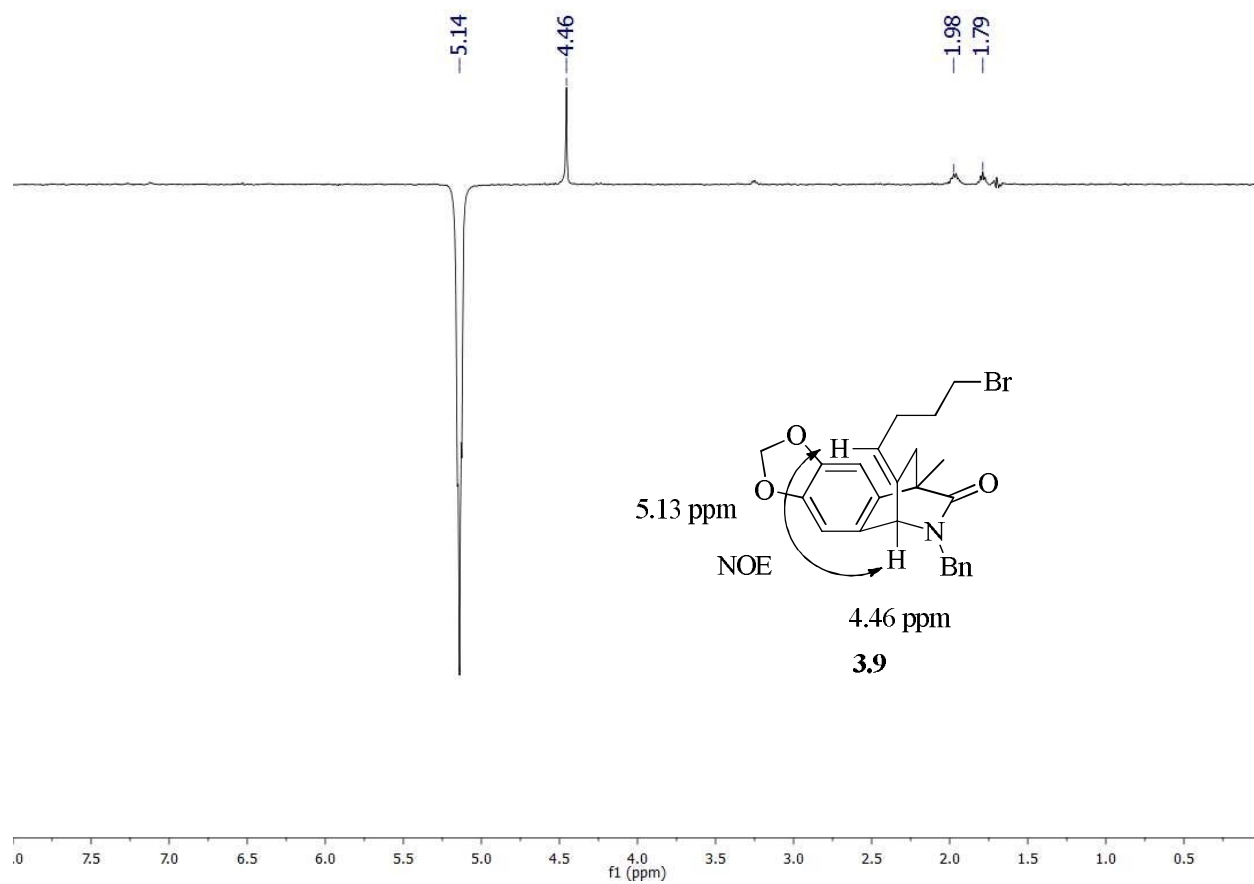
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

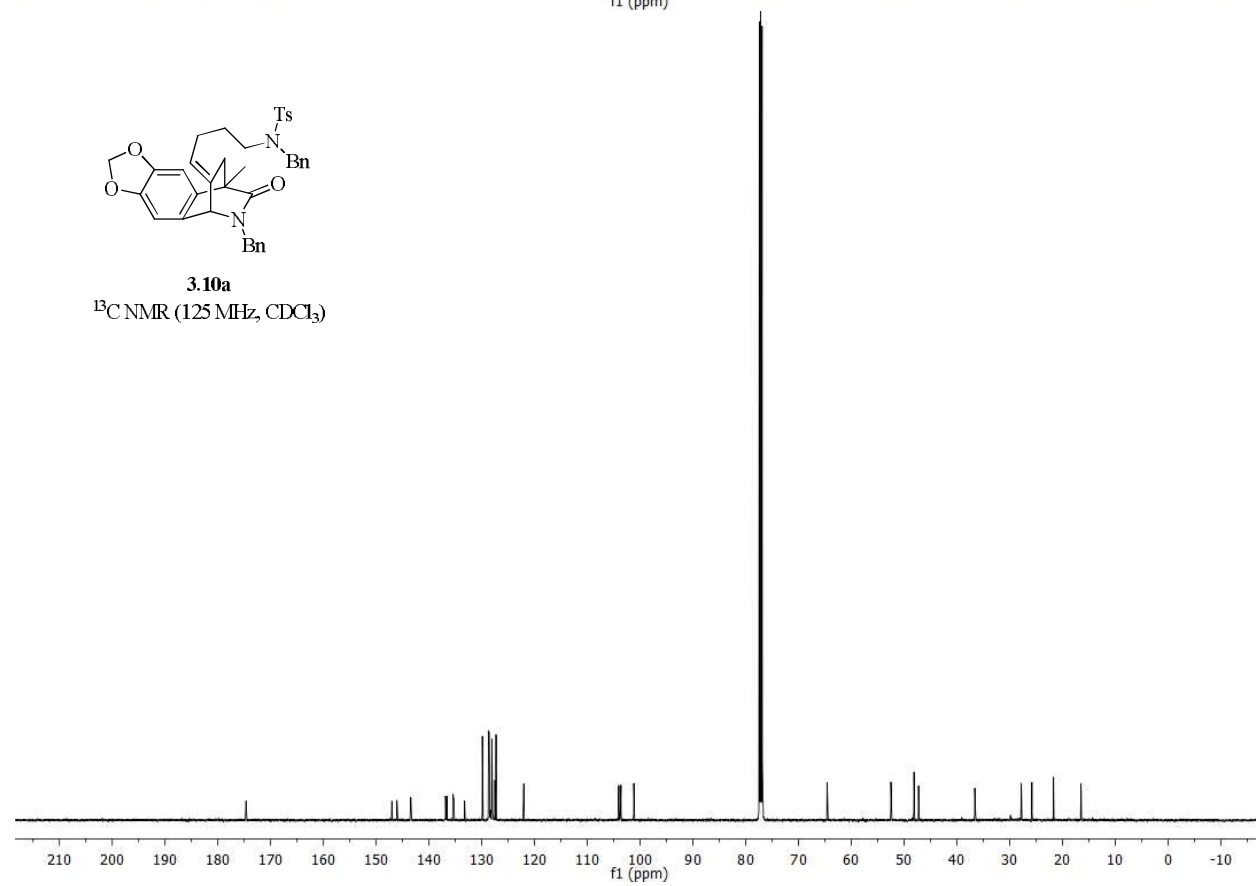
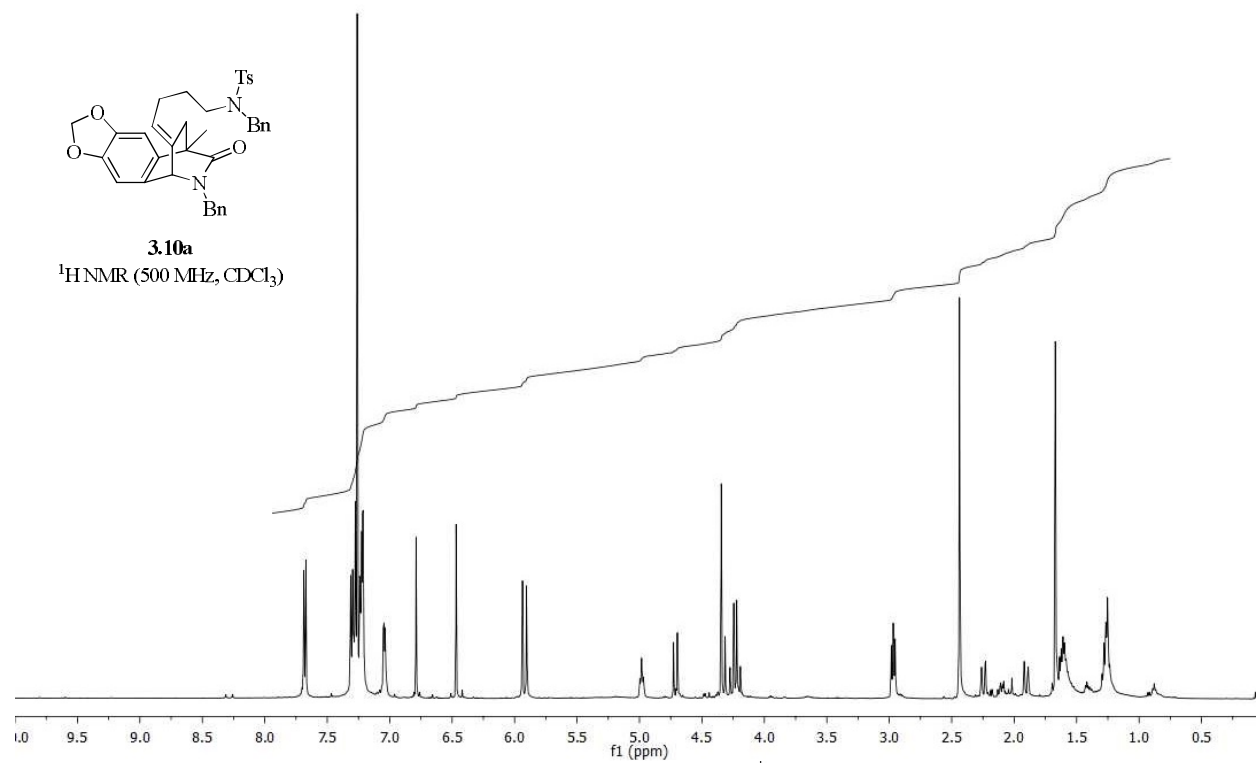


**3.9**

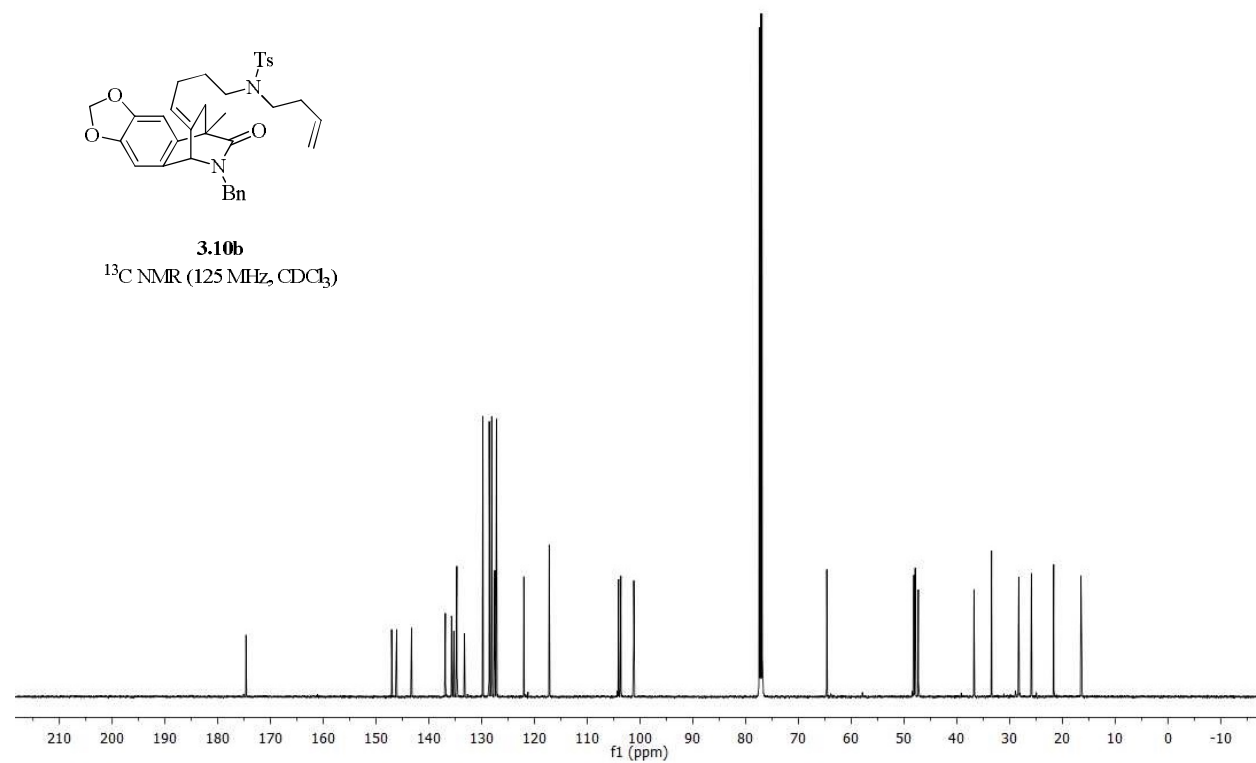
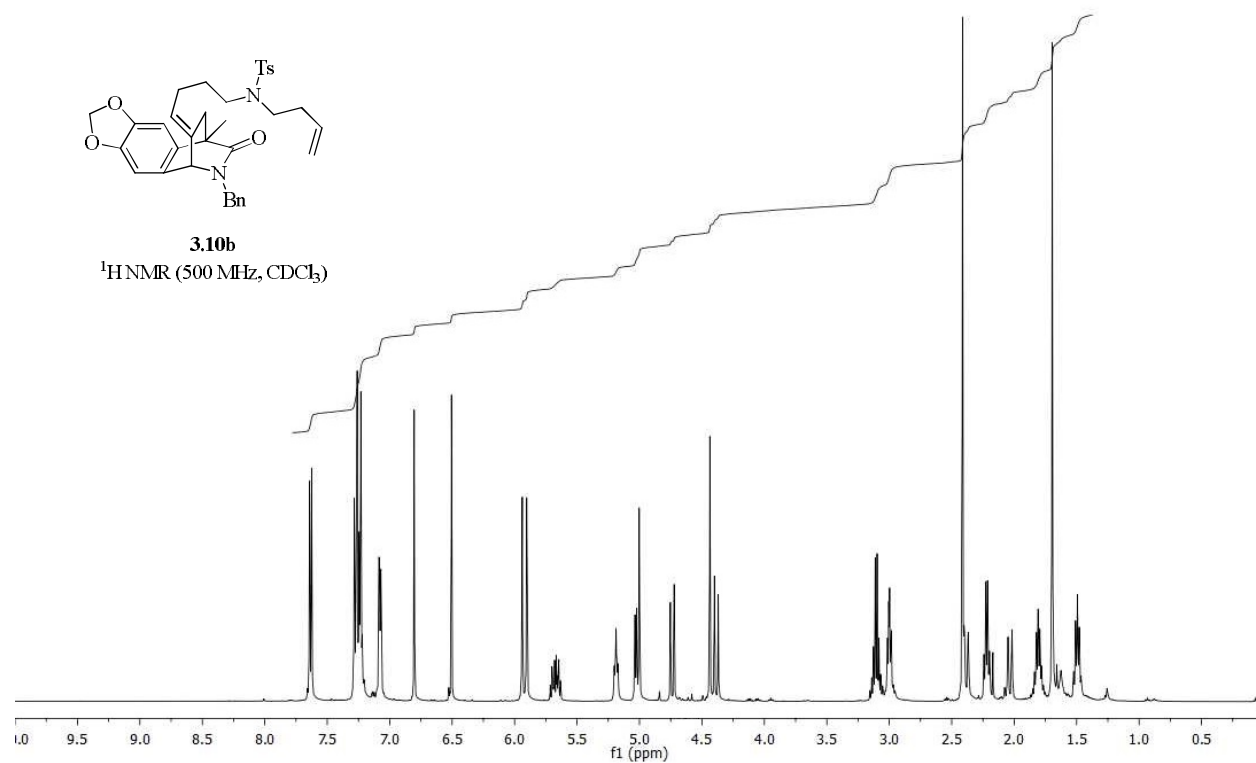
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )

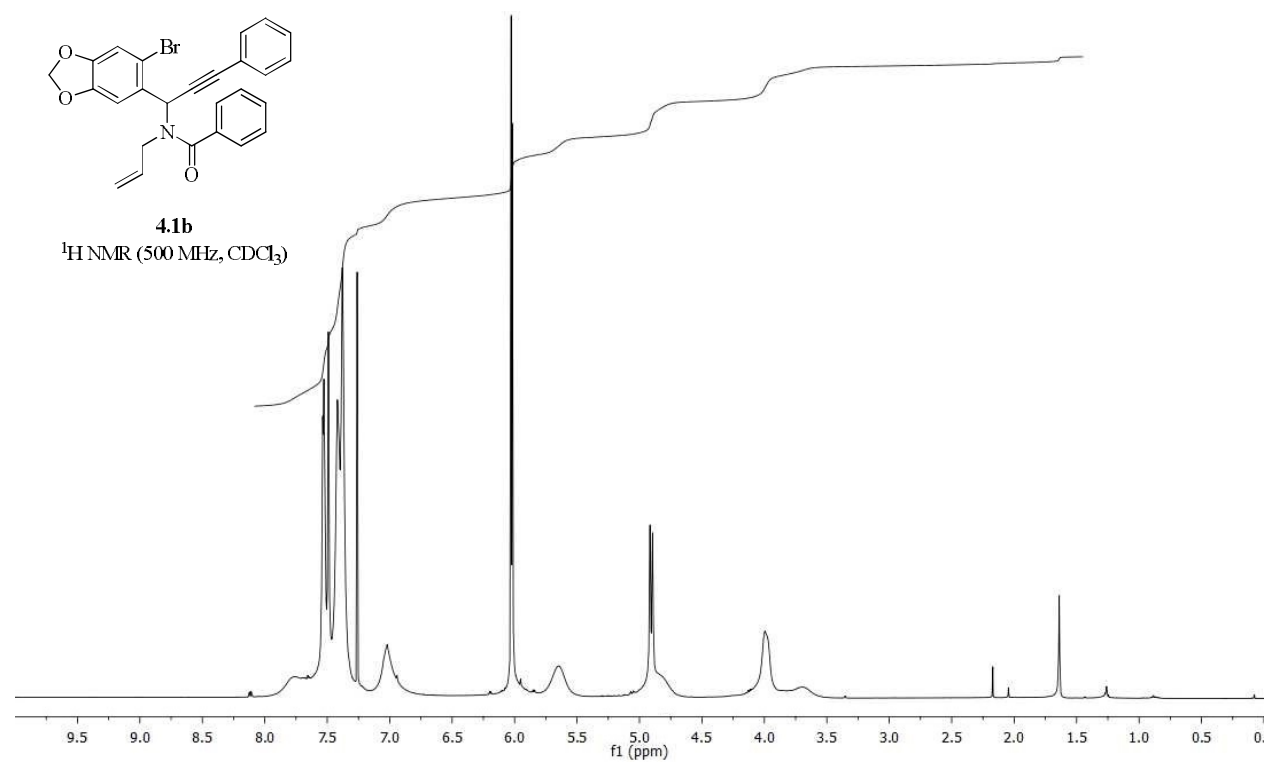
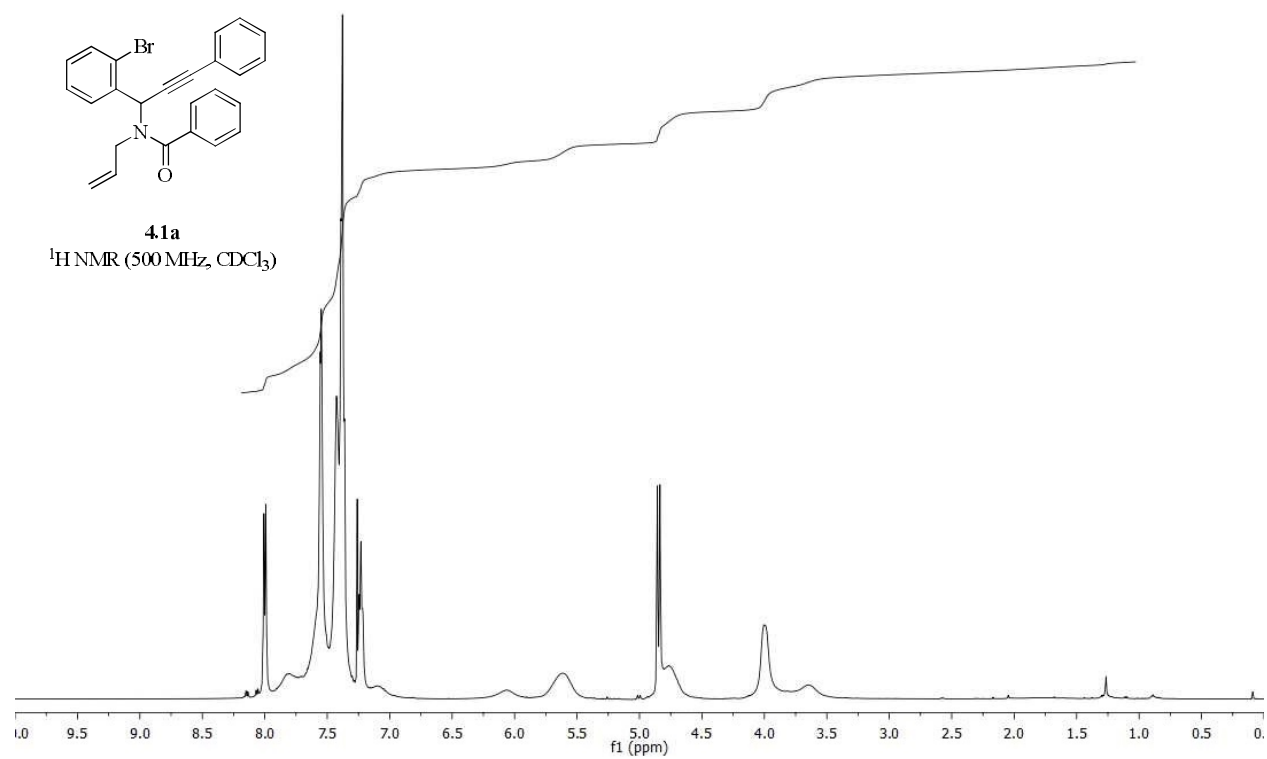


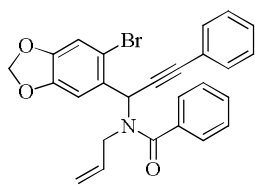






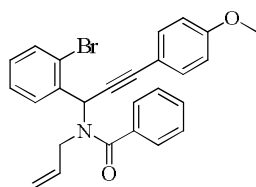
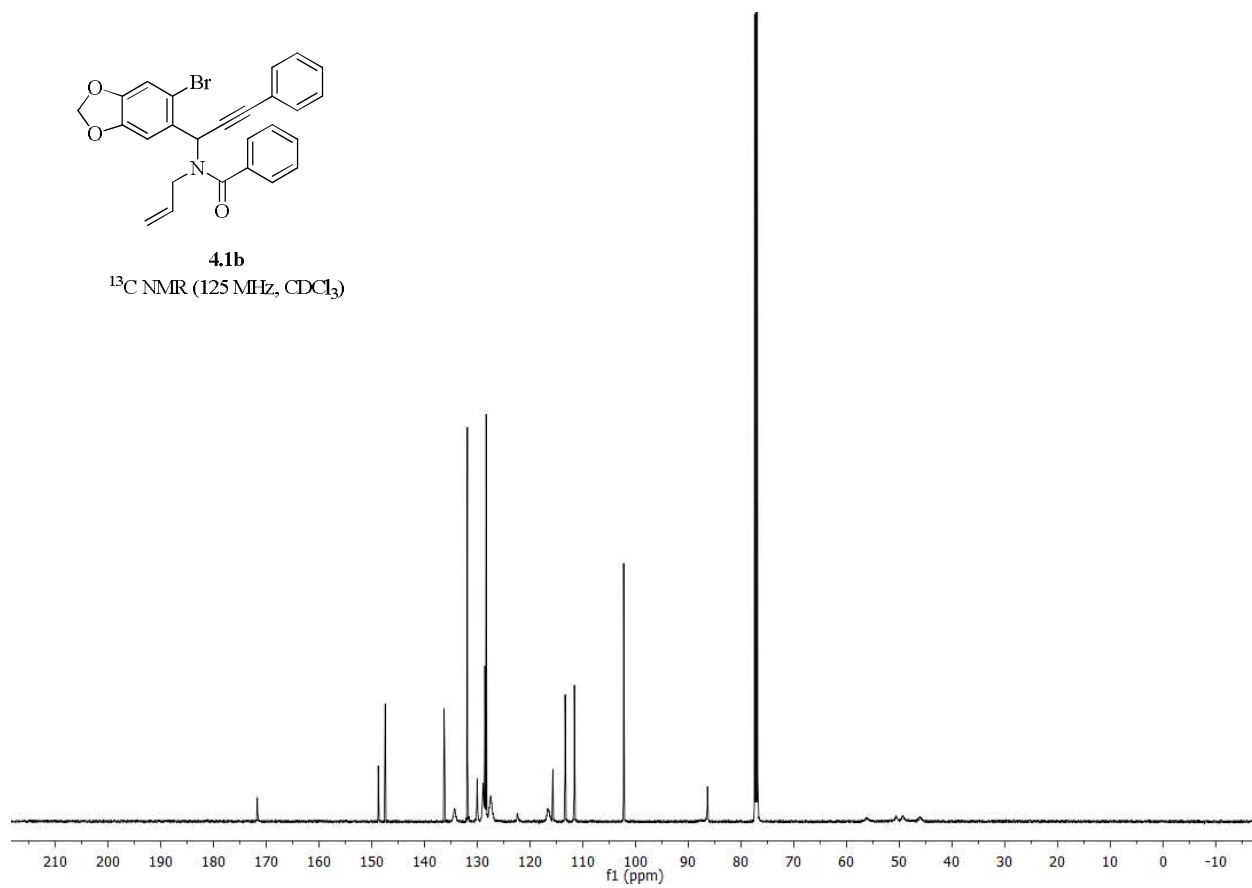






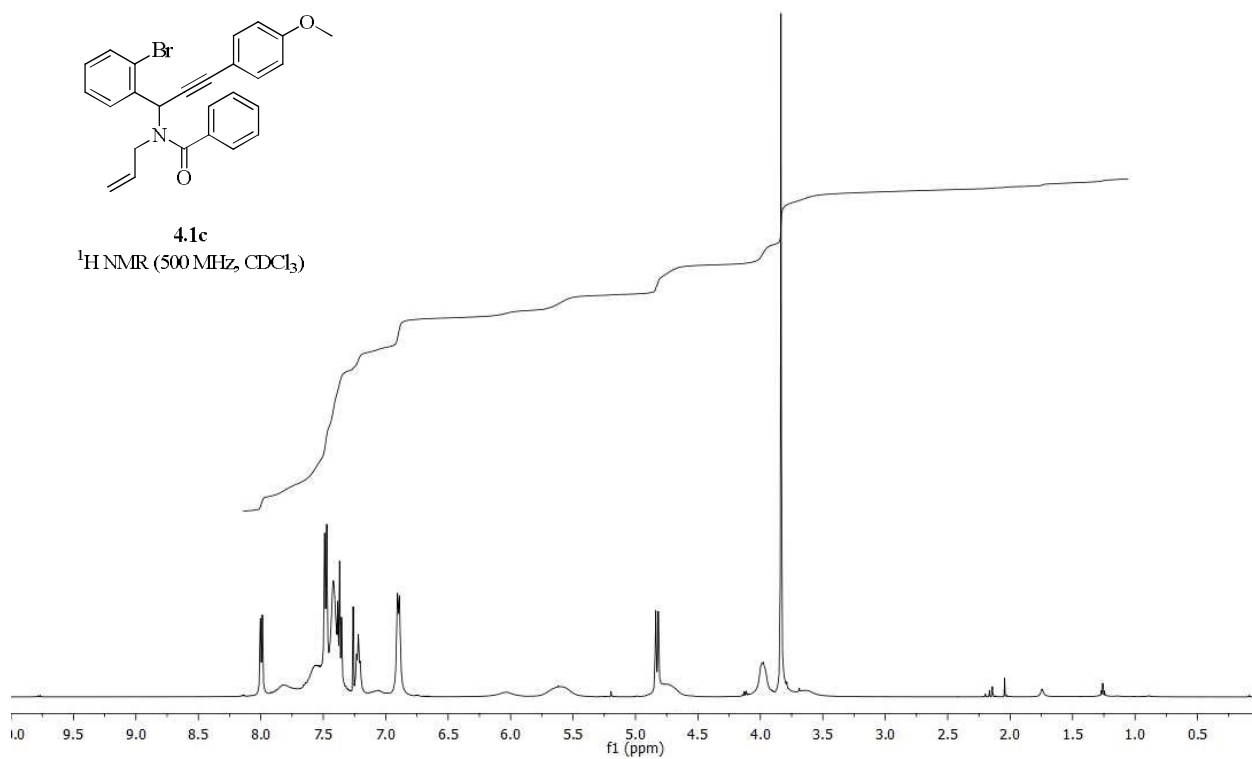
**4.1b**

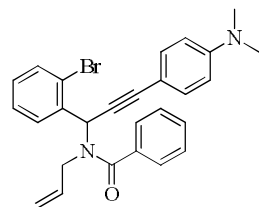
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )



**4.1c**

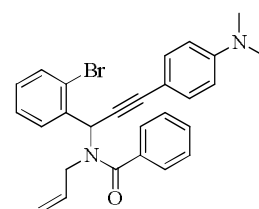
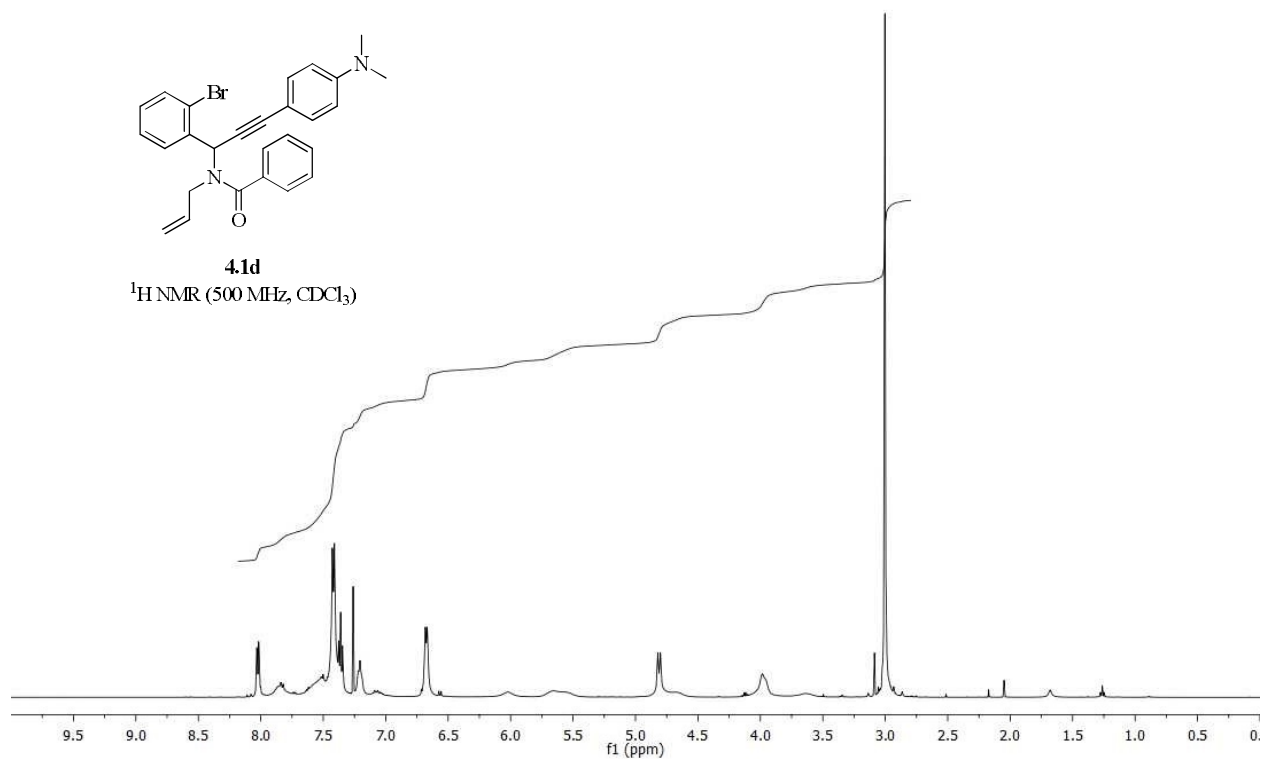
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )





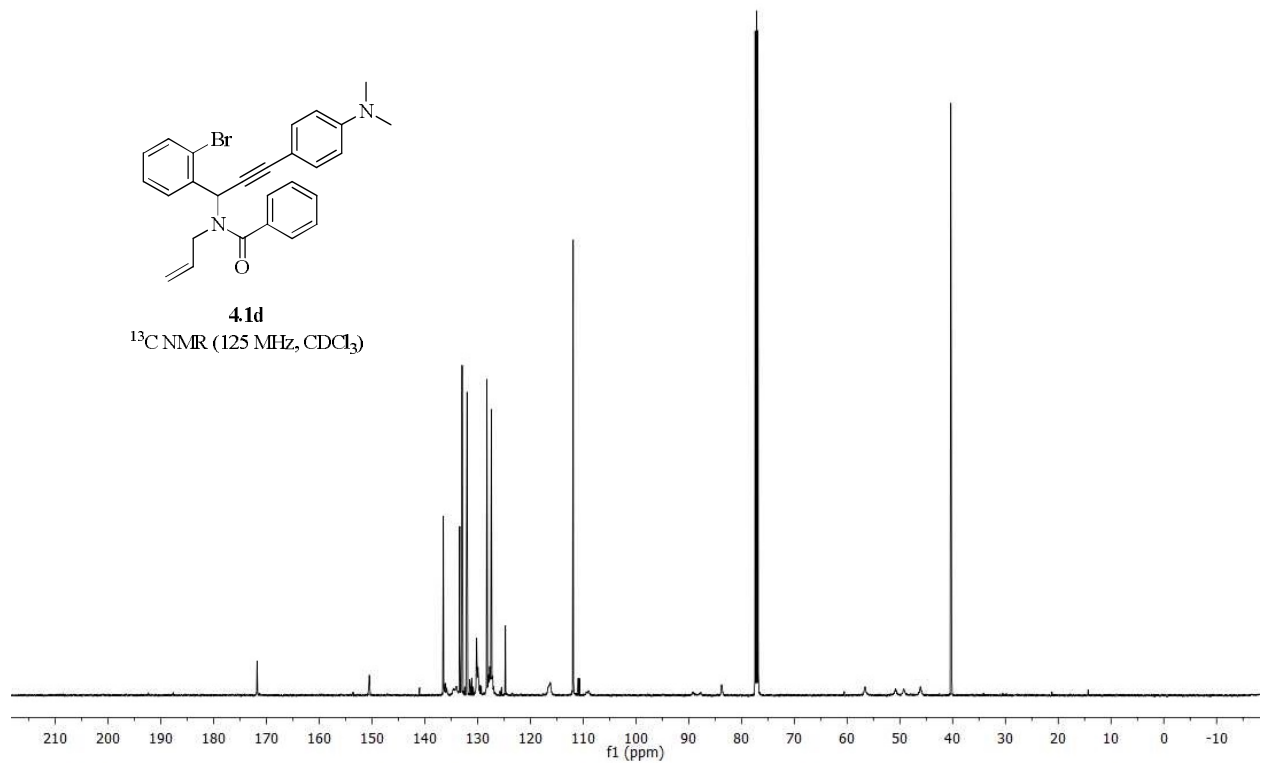
**4.1d**

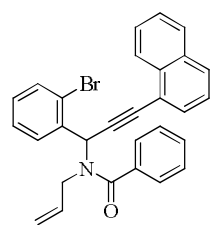
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



**4.1d**

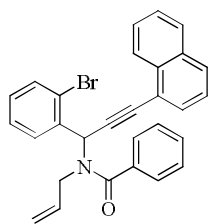
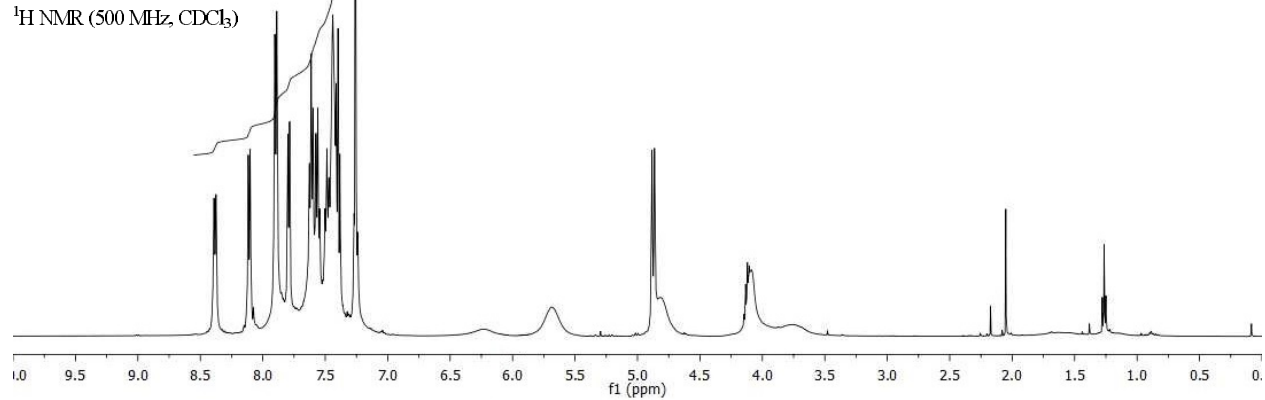
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )





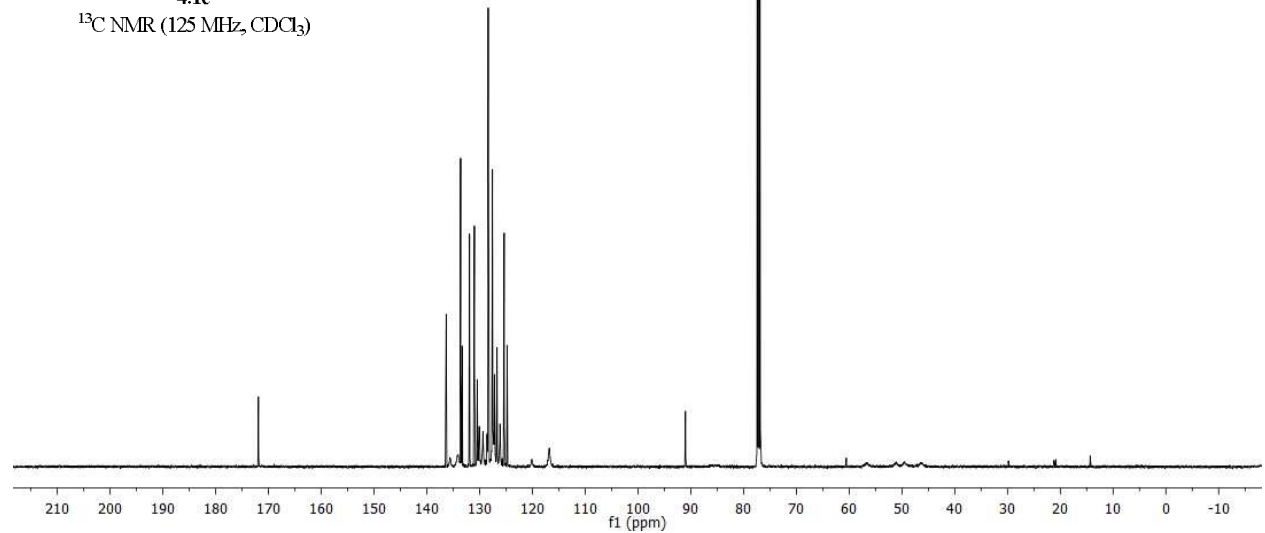
**4.1e**

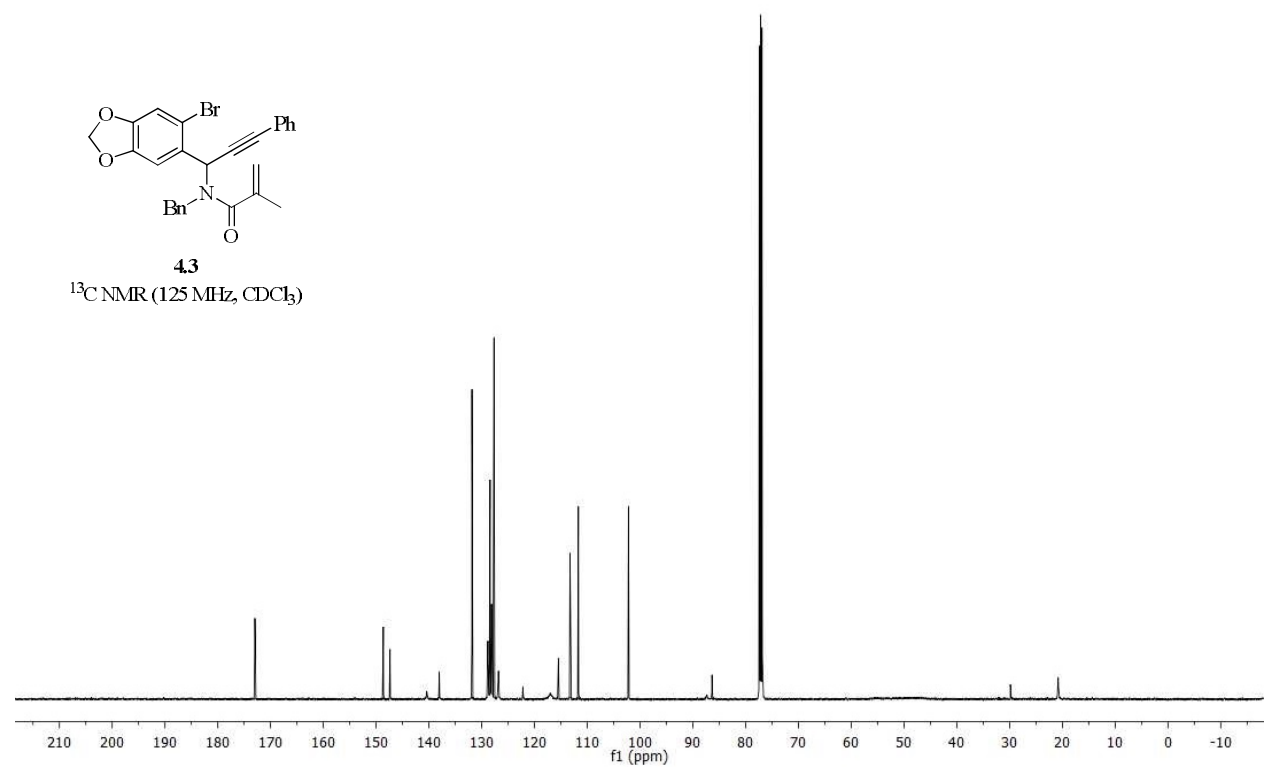
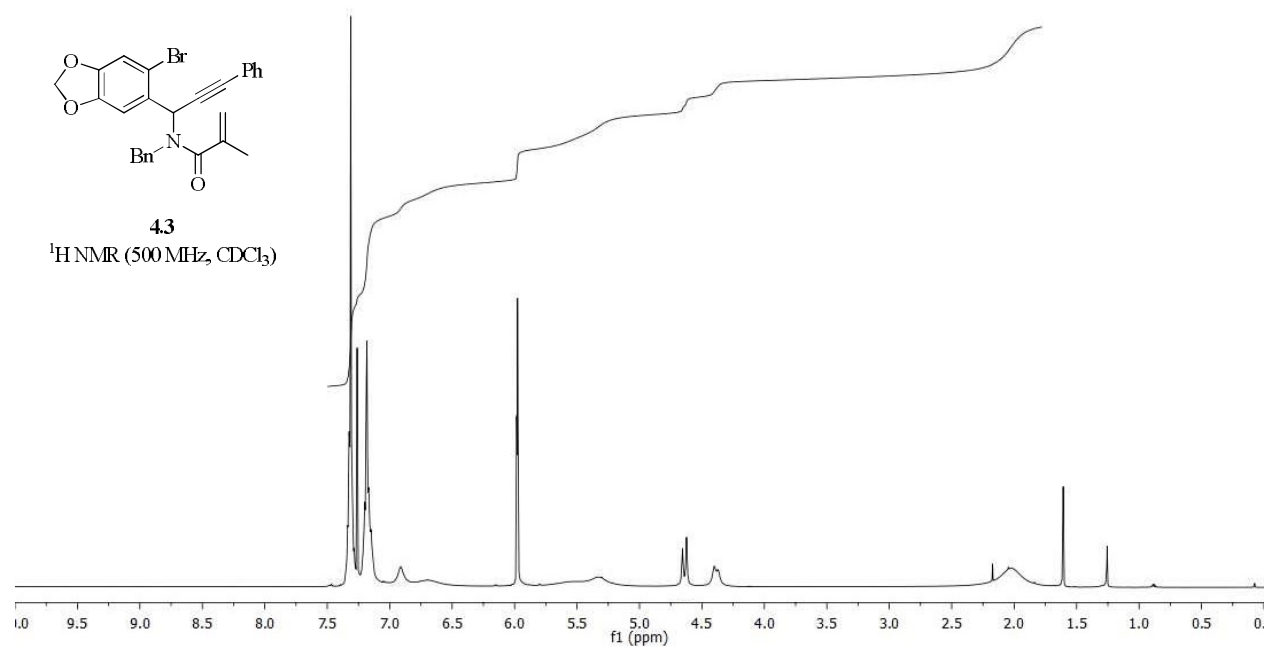
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

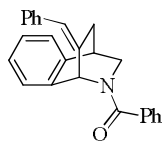


**4.1e**

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )

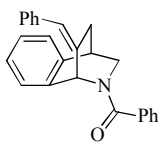
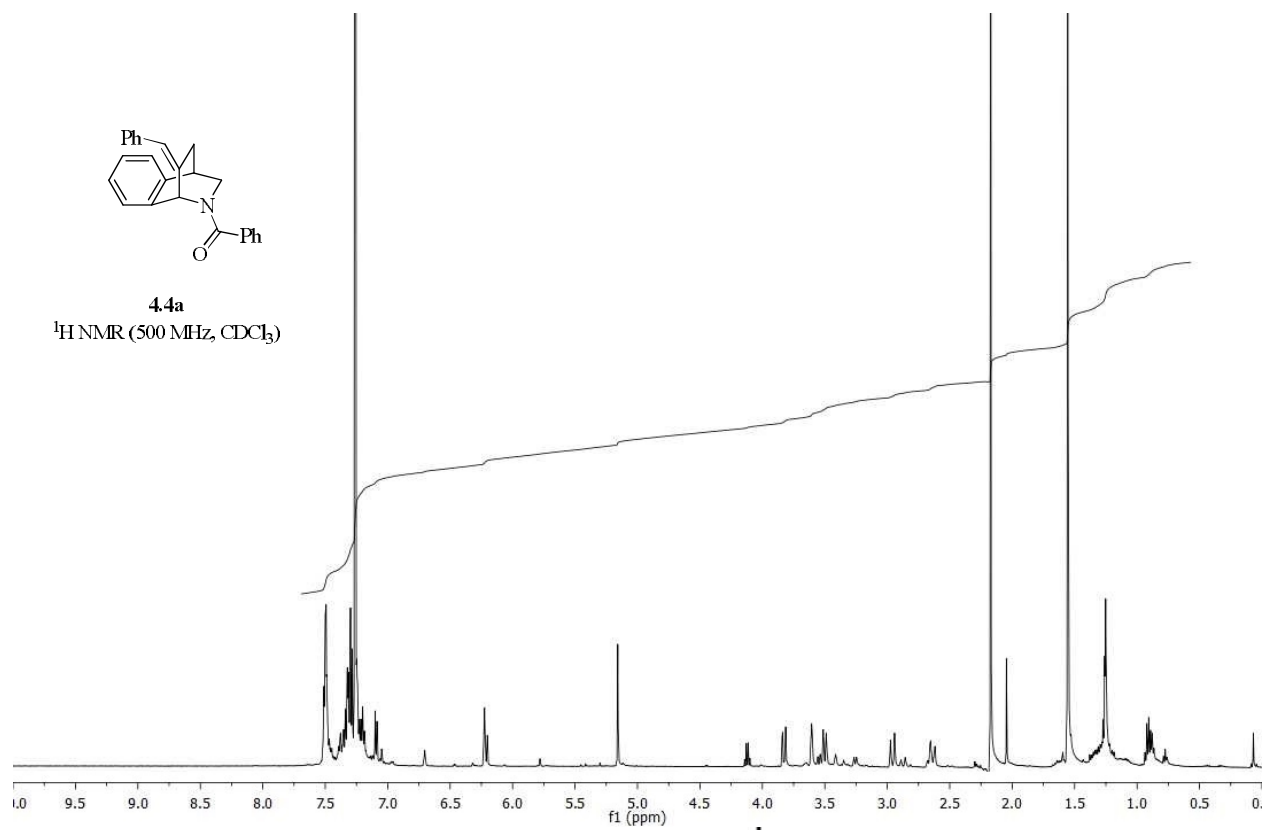






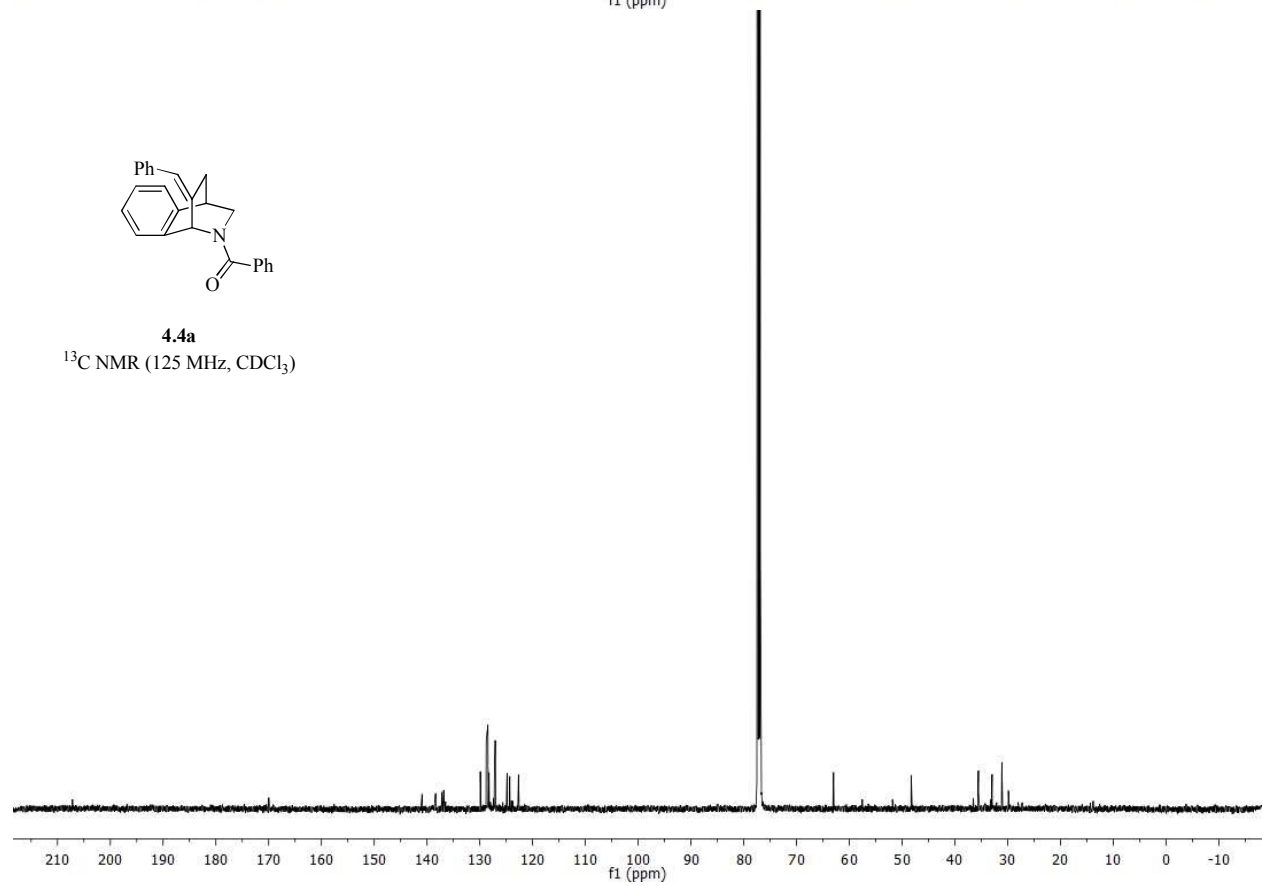
**4.4a**

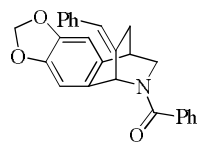
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



**4.4a**

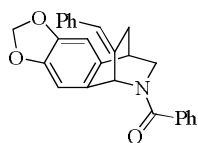
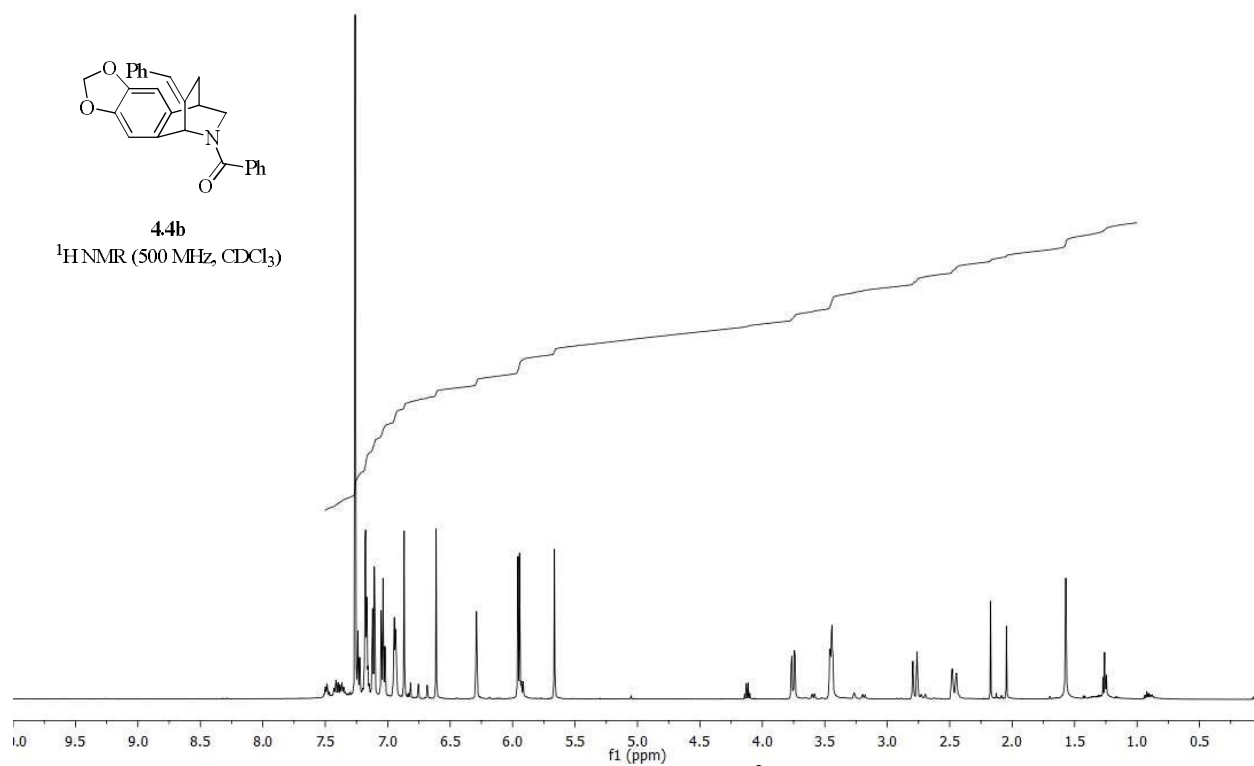
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )





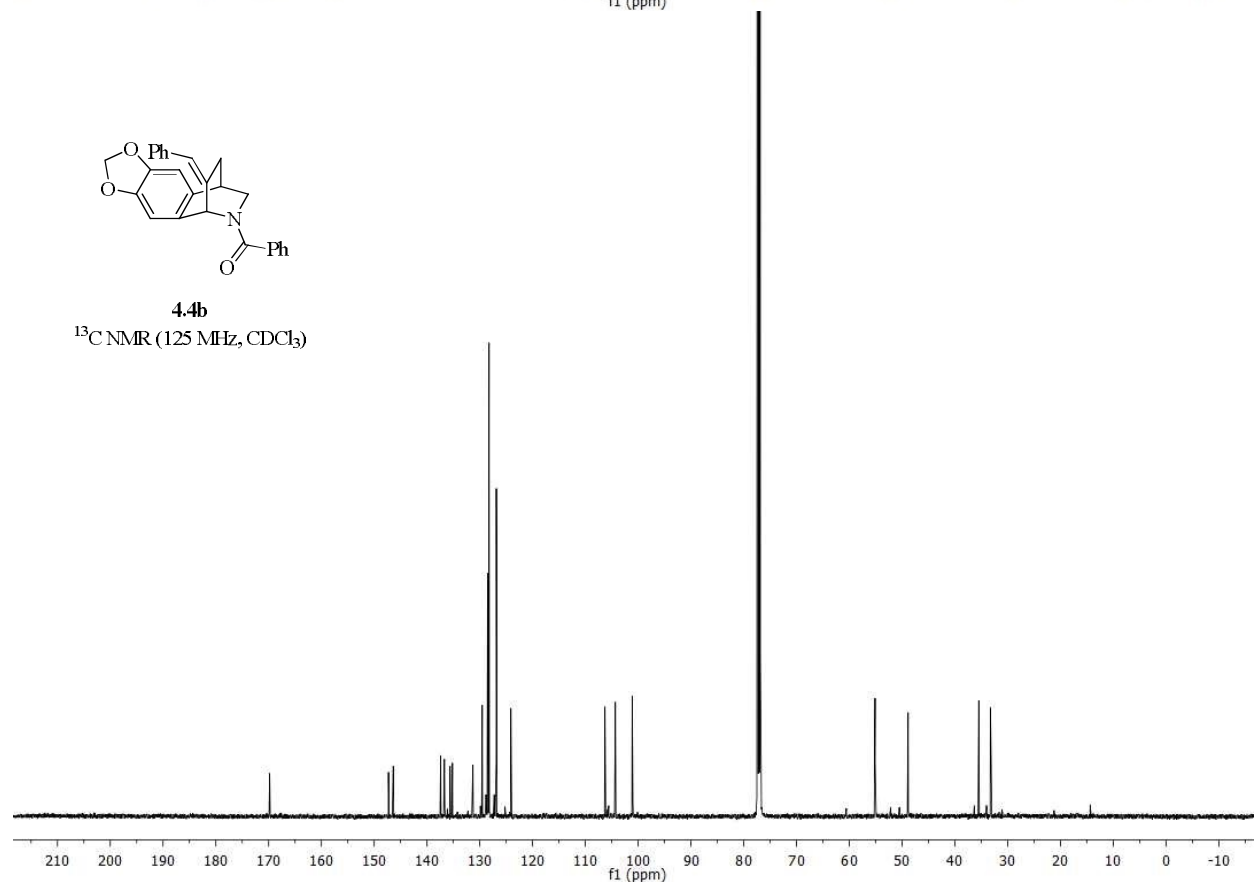
**4.4b**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

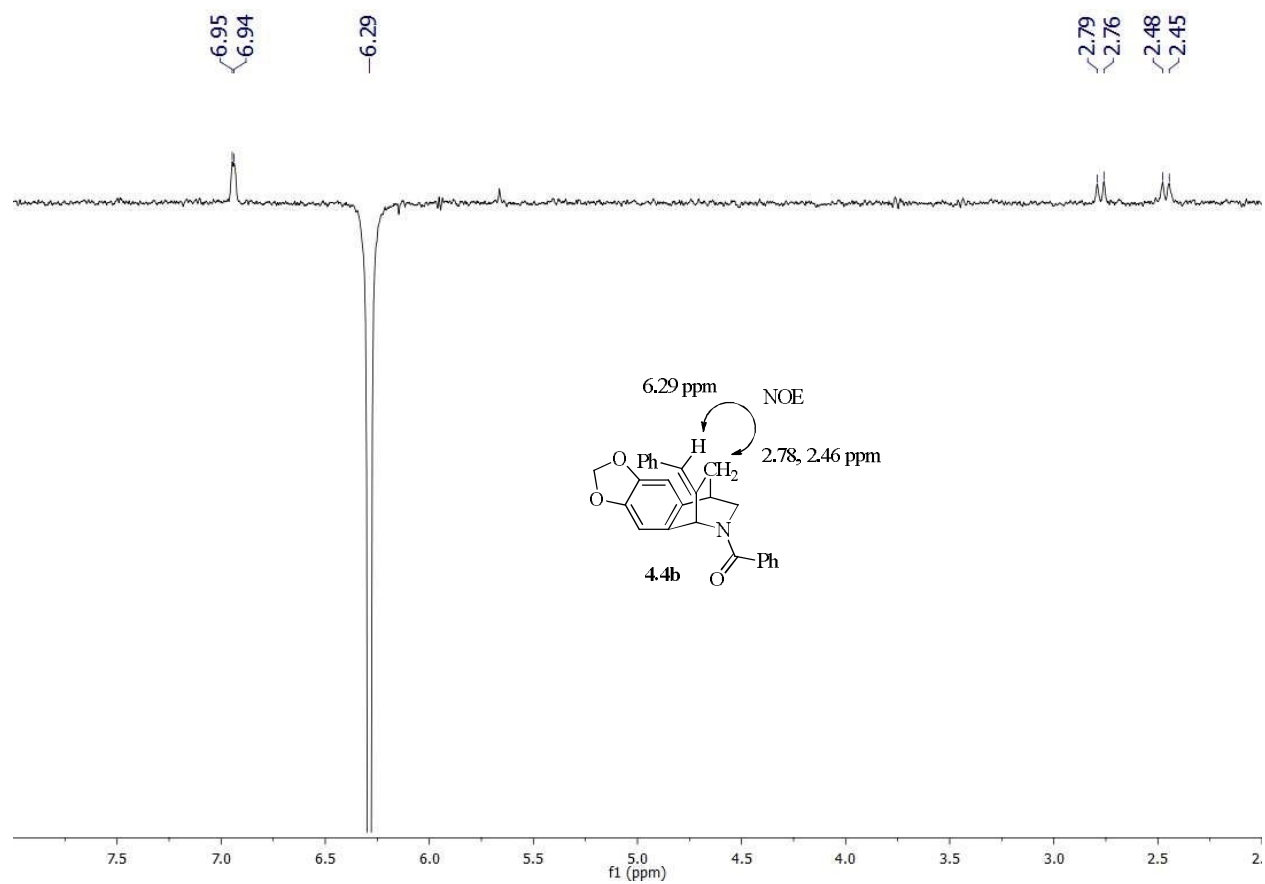


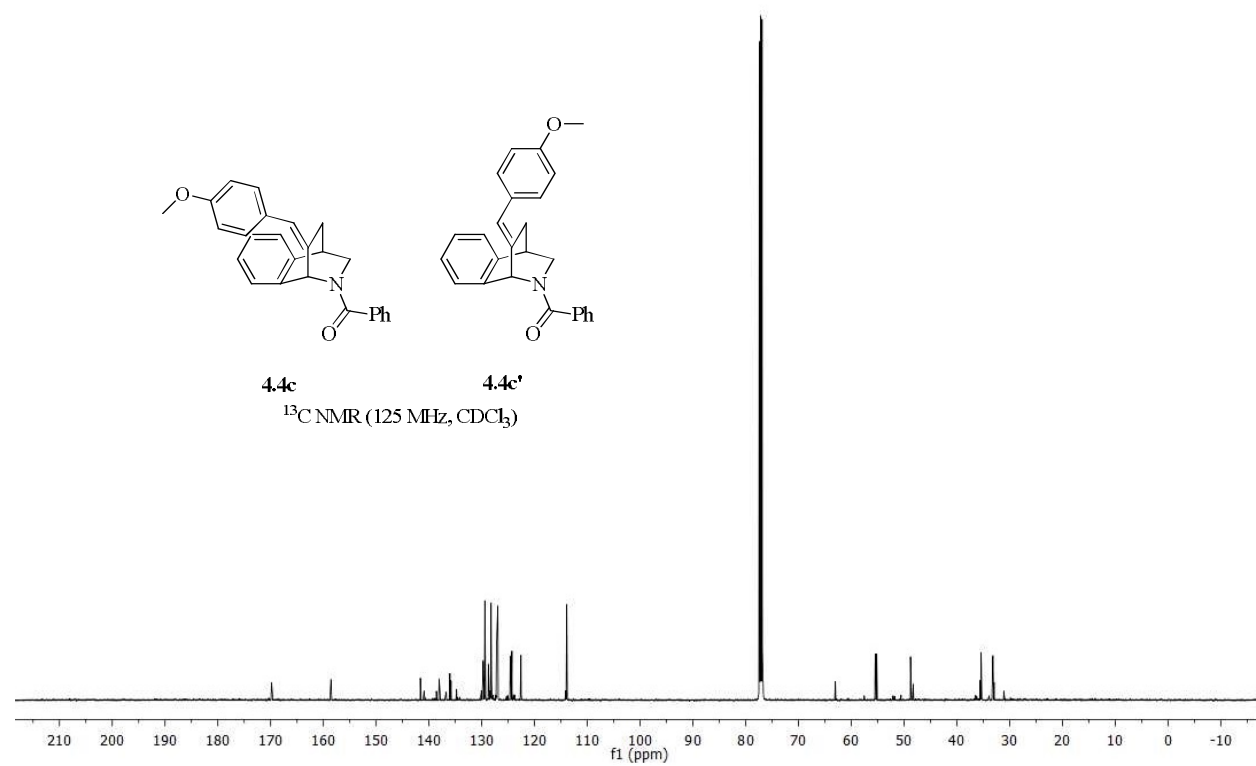
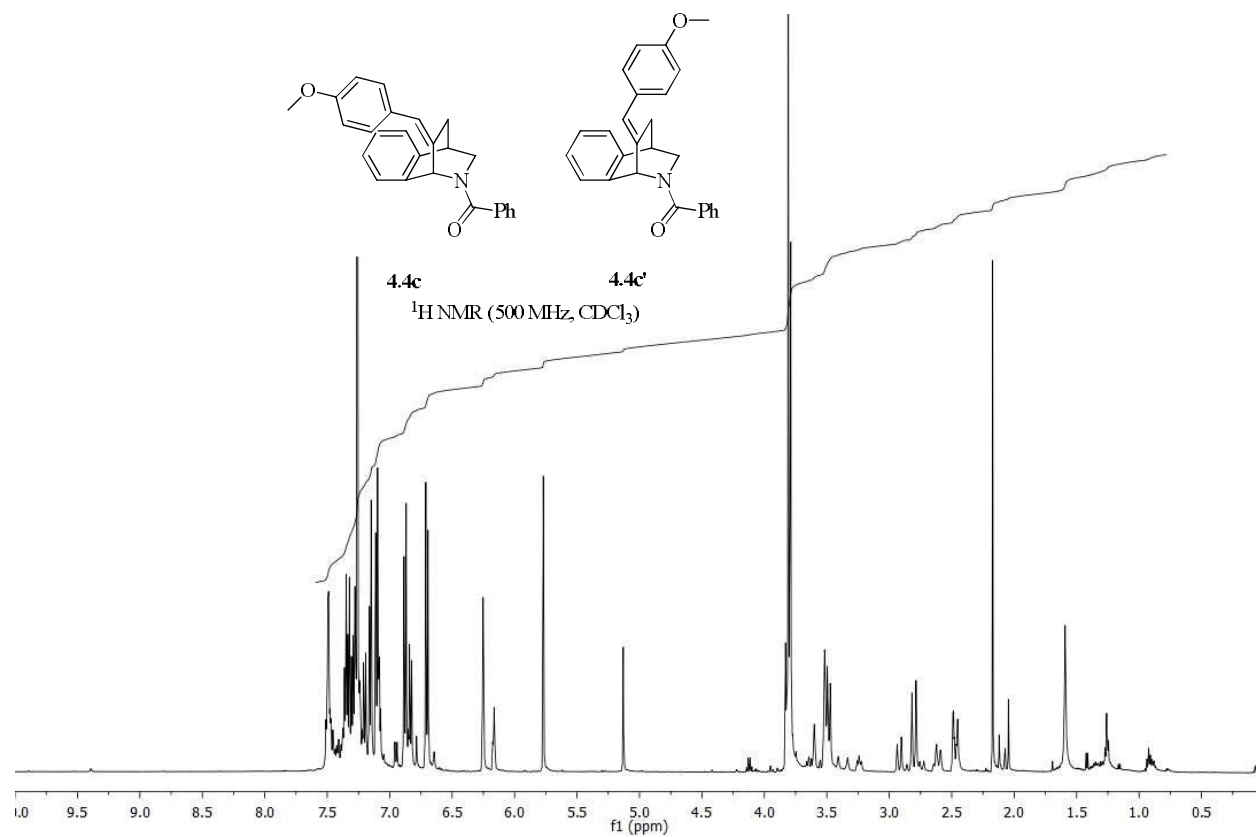
**4.4b**

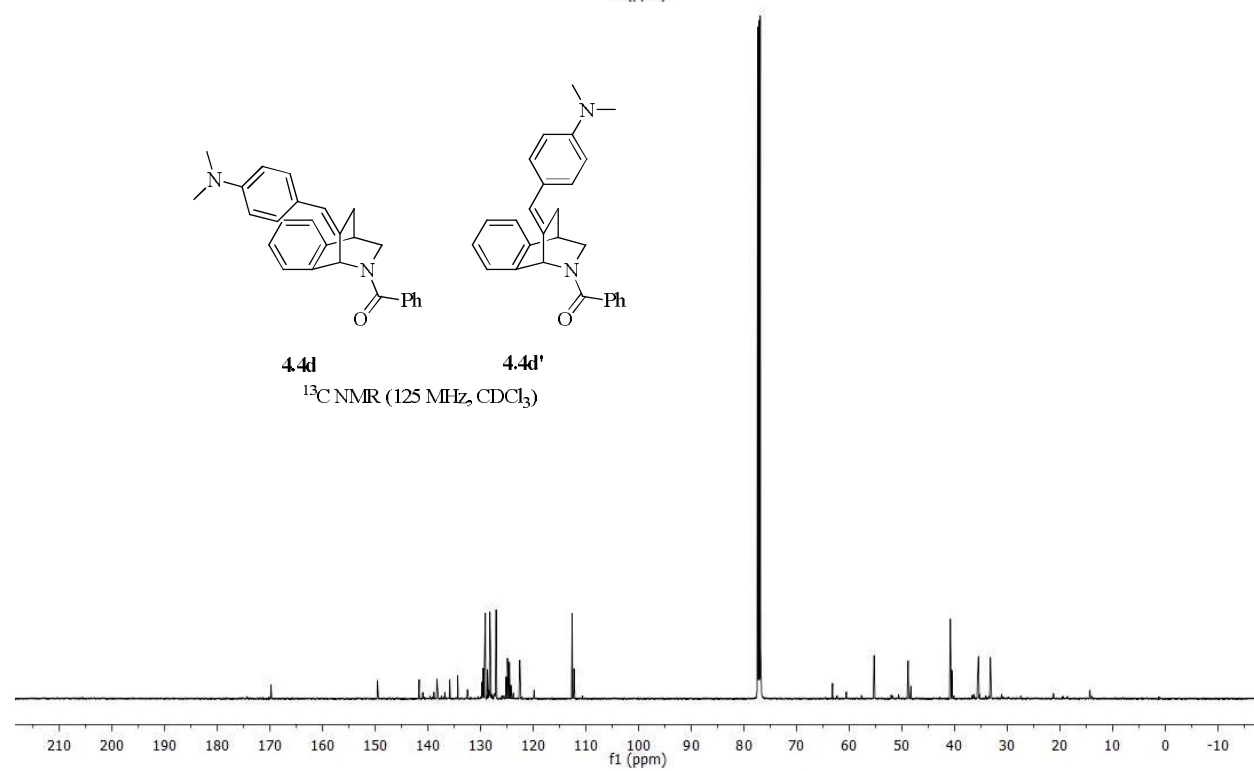
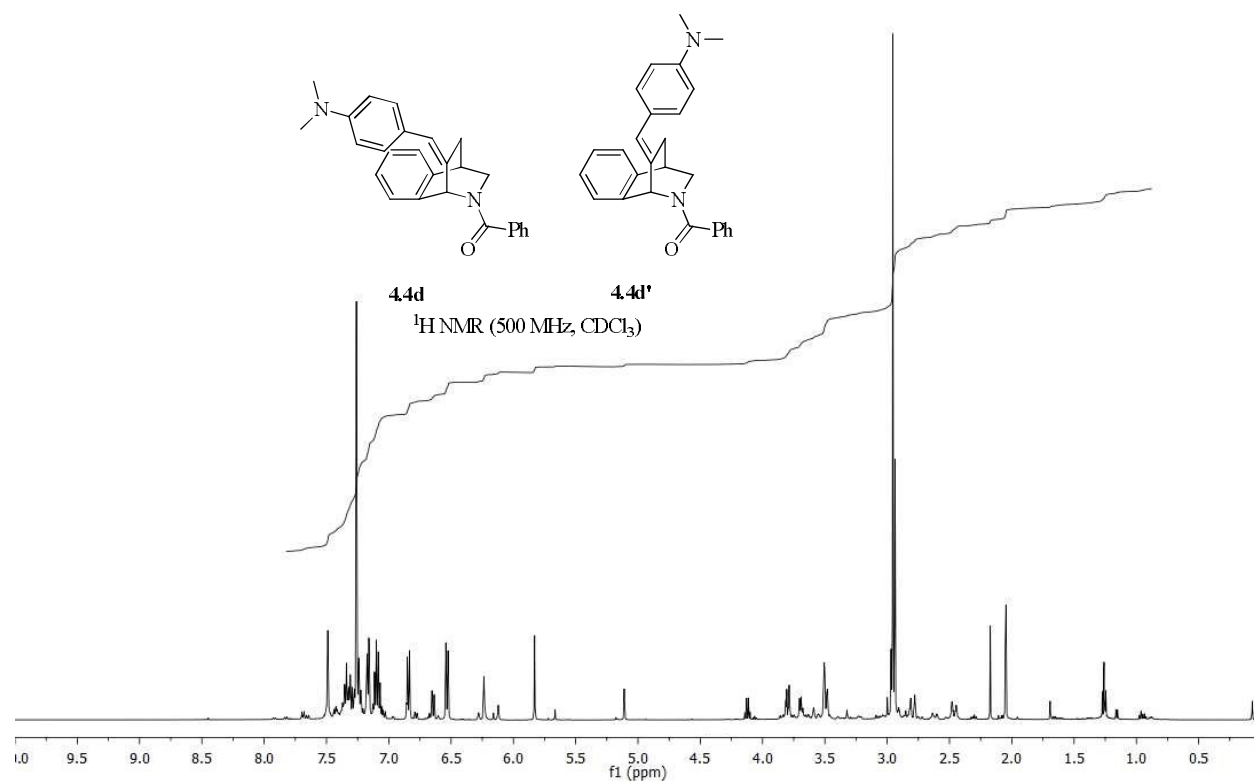
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )

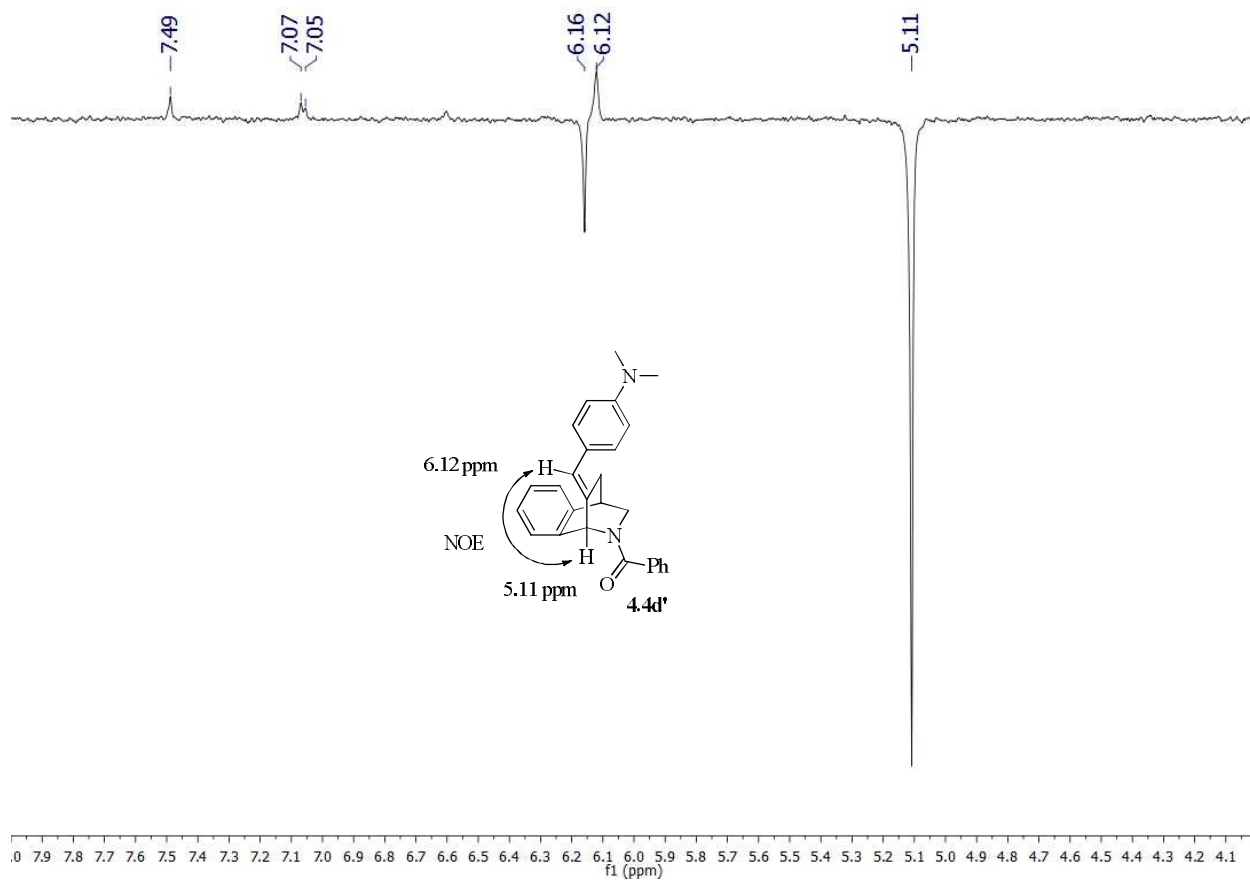


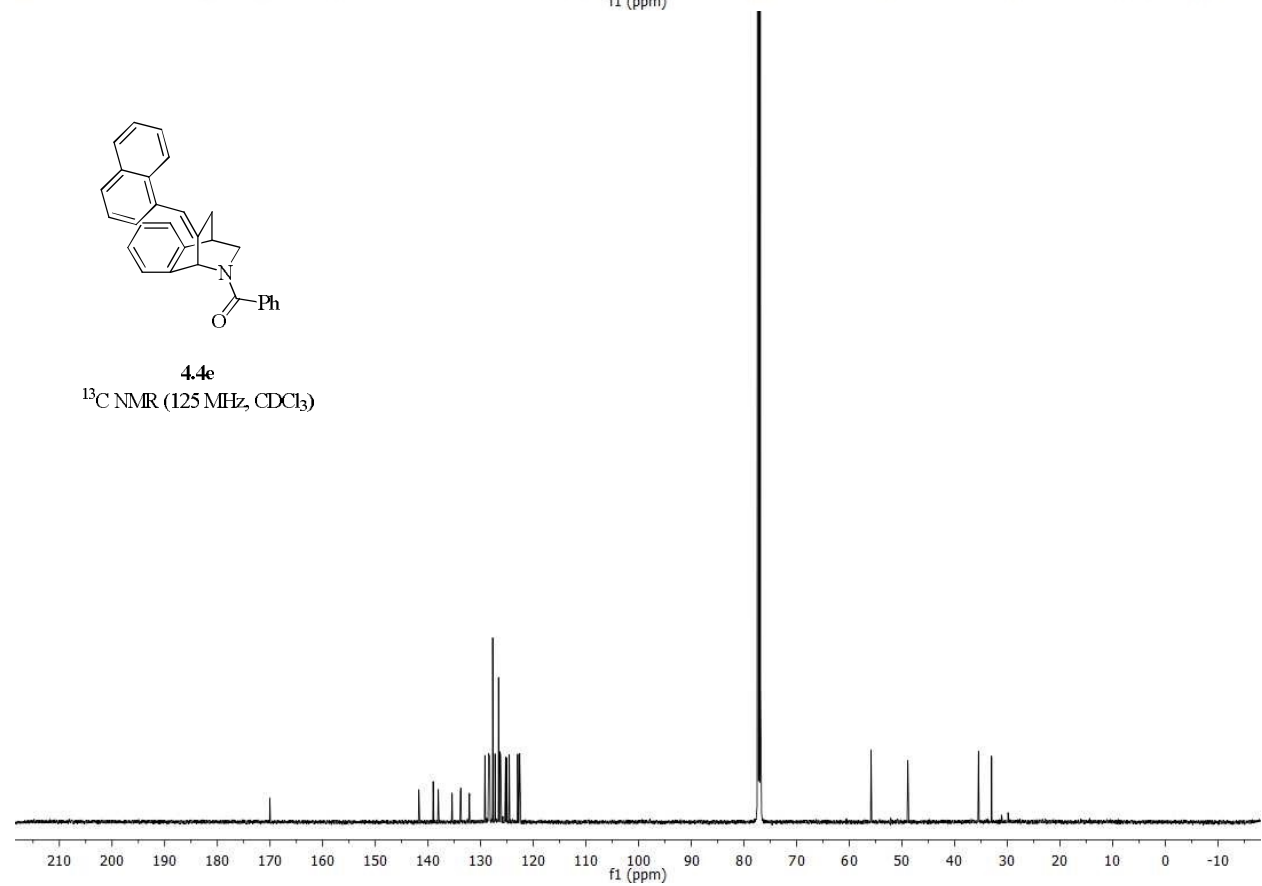
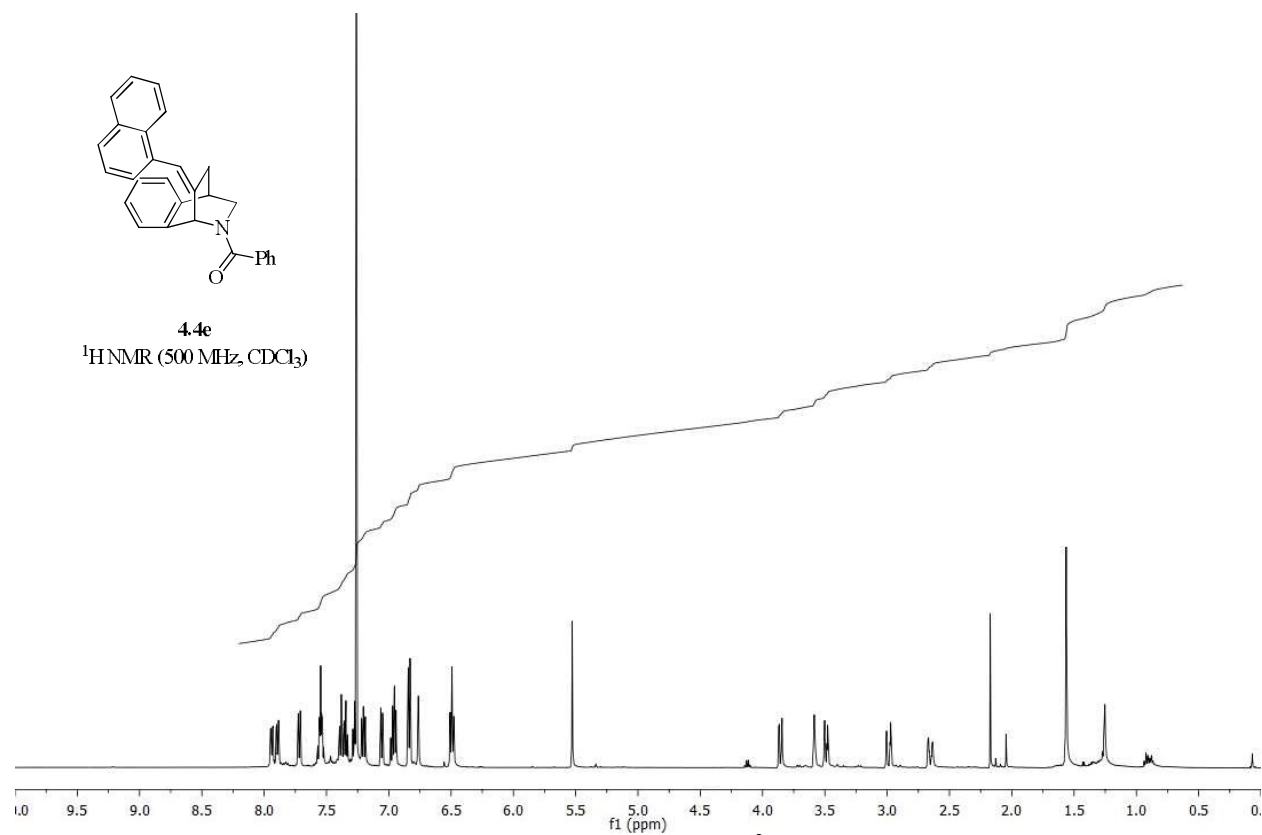


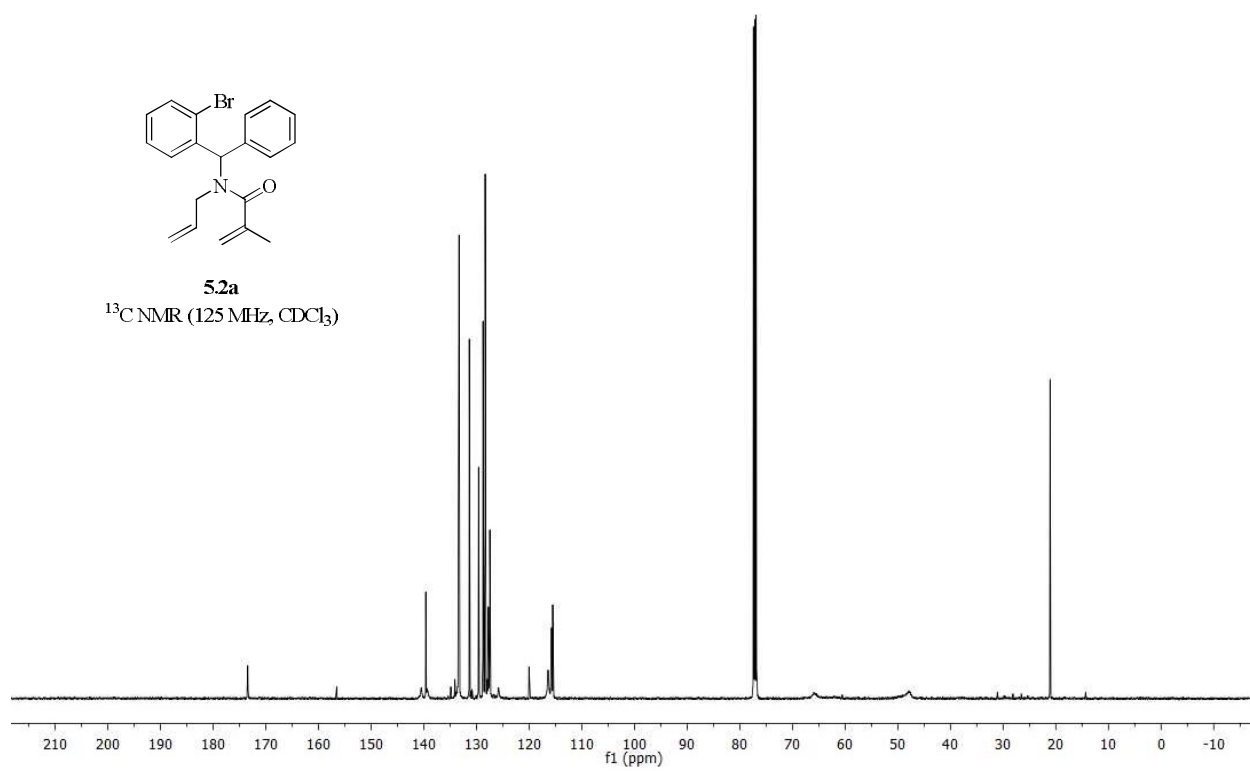
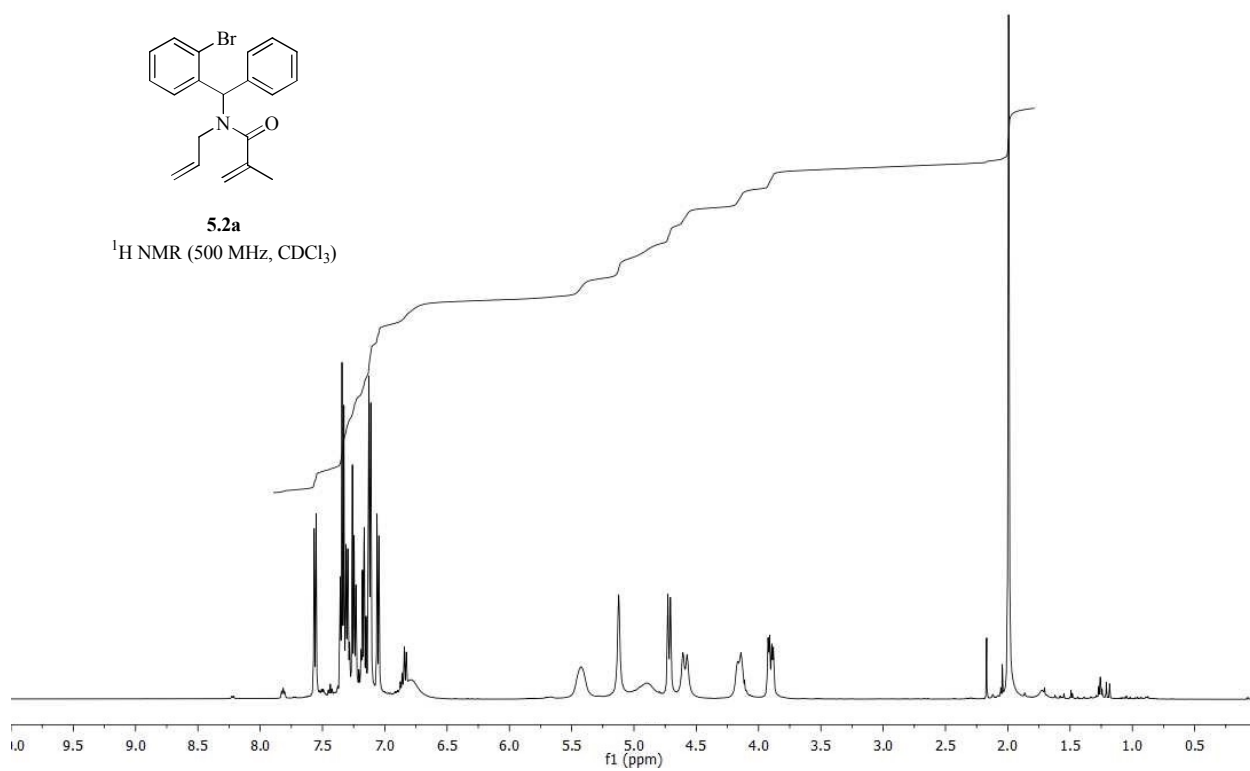


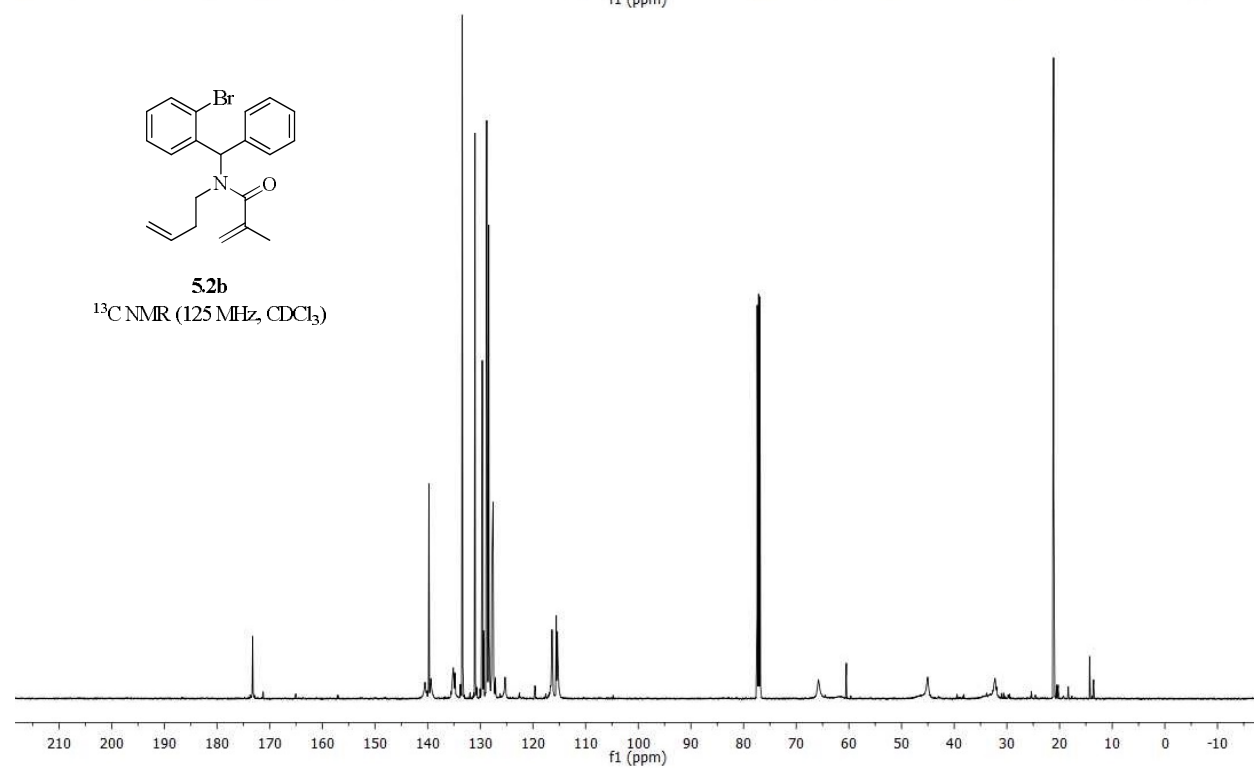
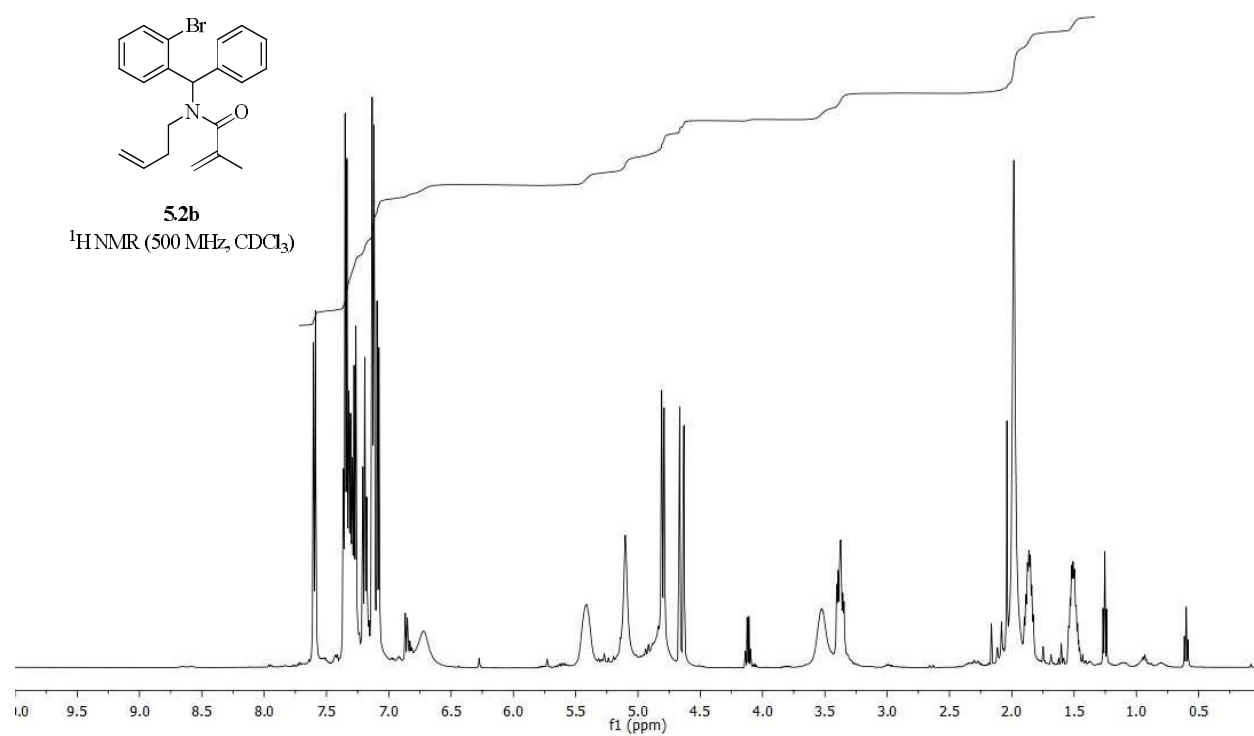


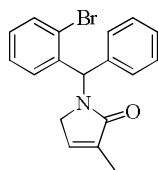






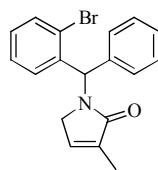
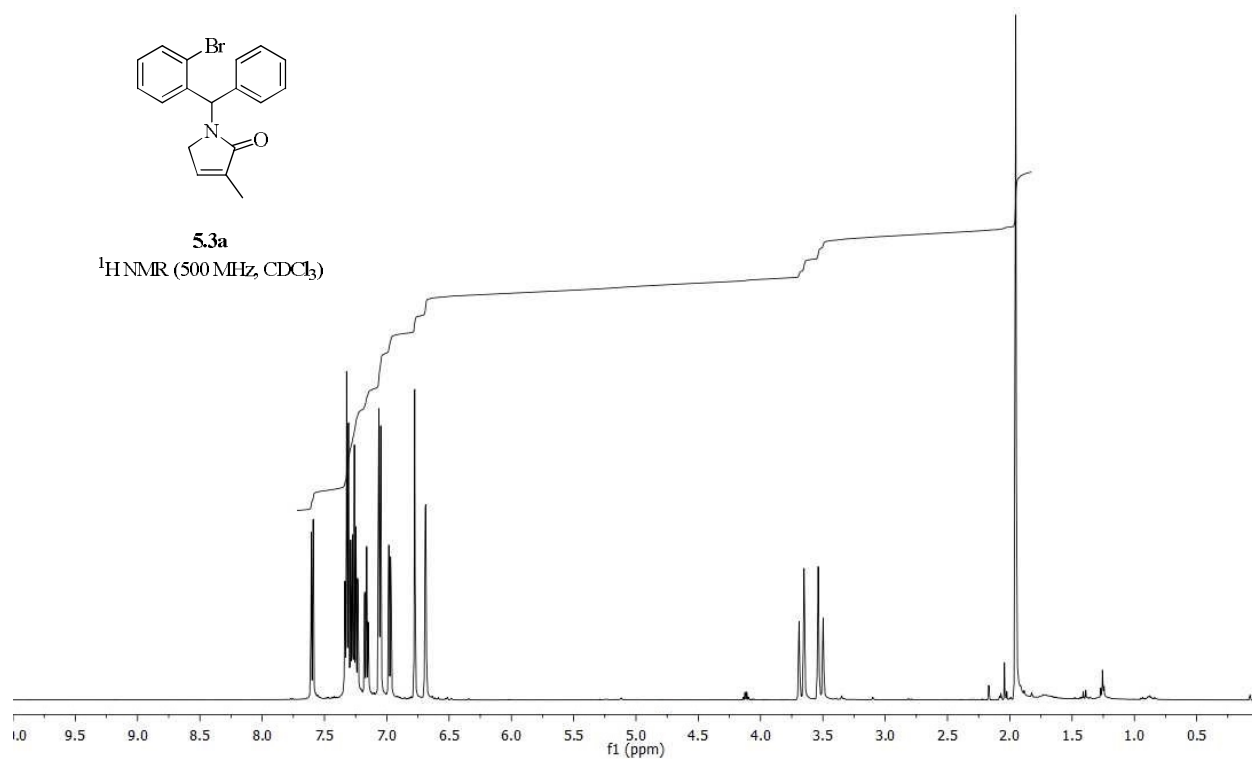






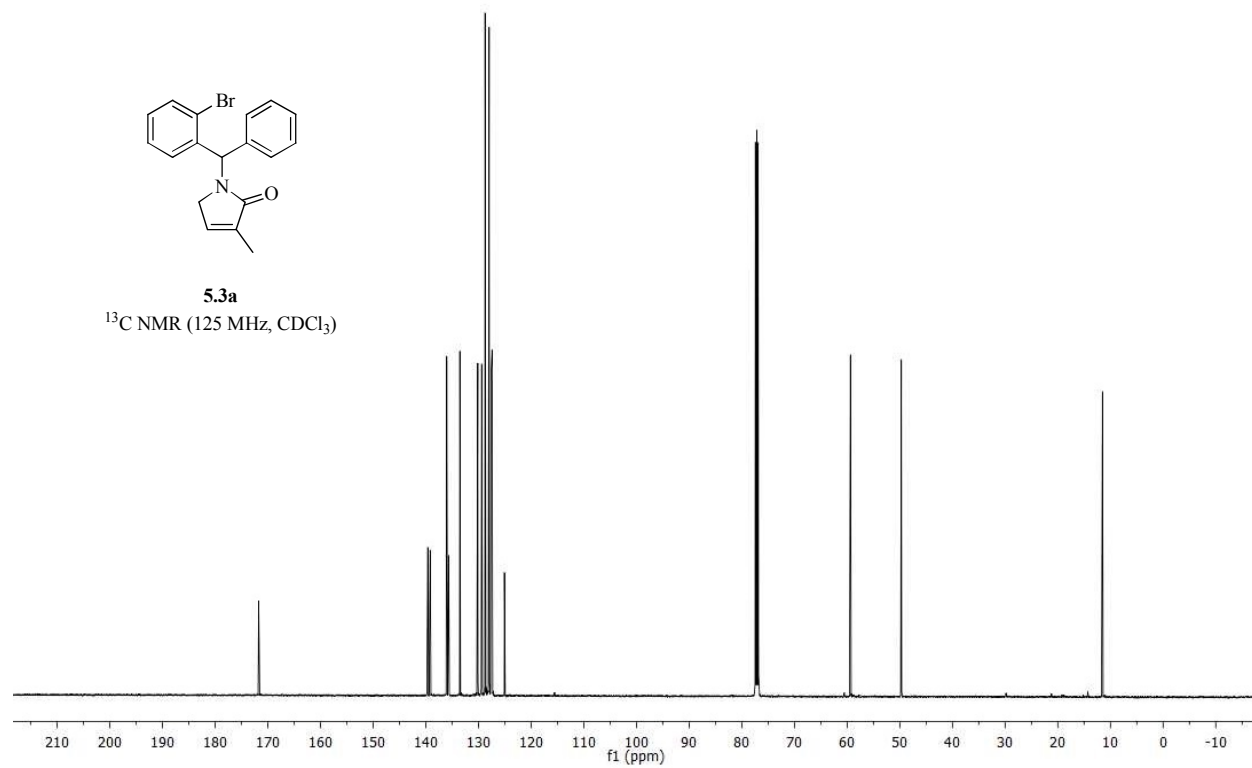
**5.3a**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

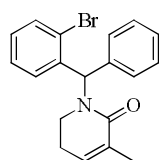


**5.3a**

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )

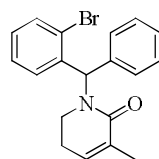
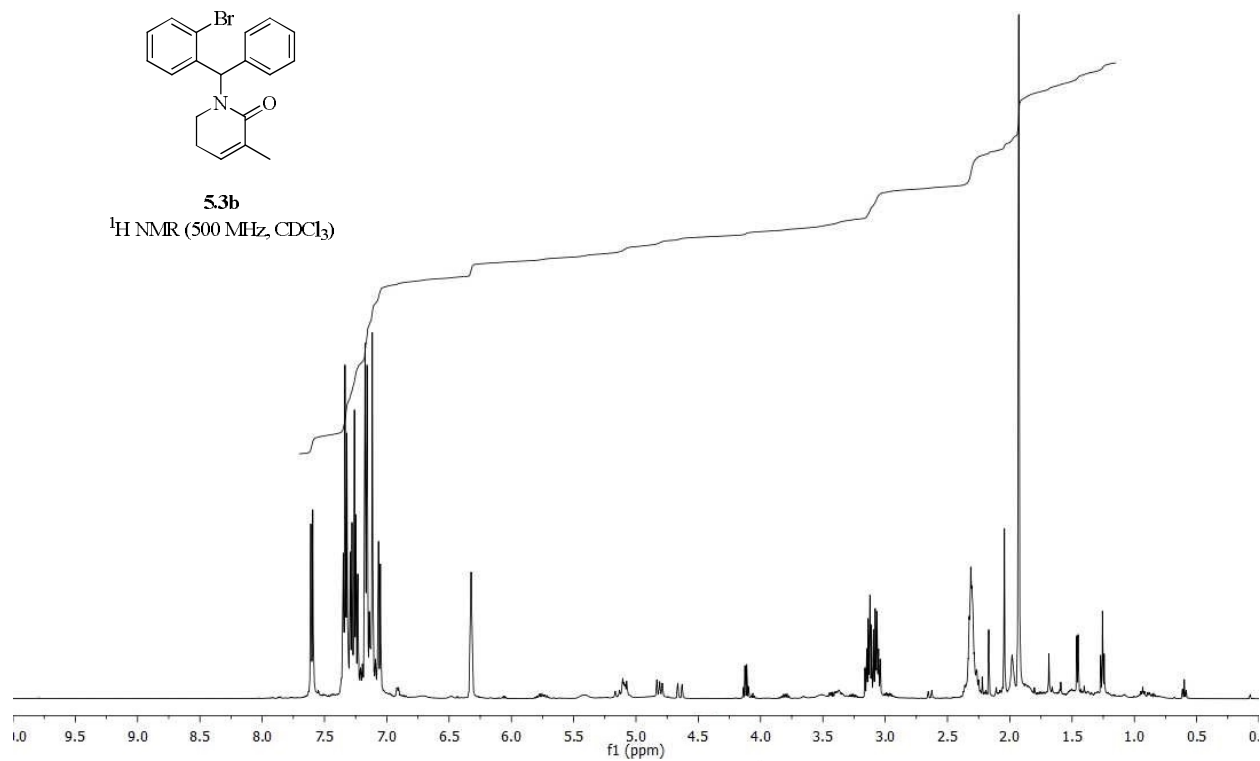






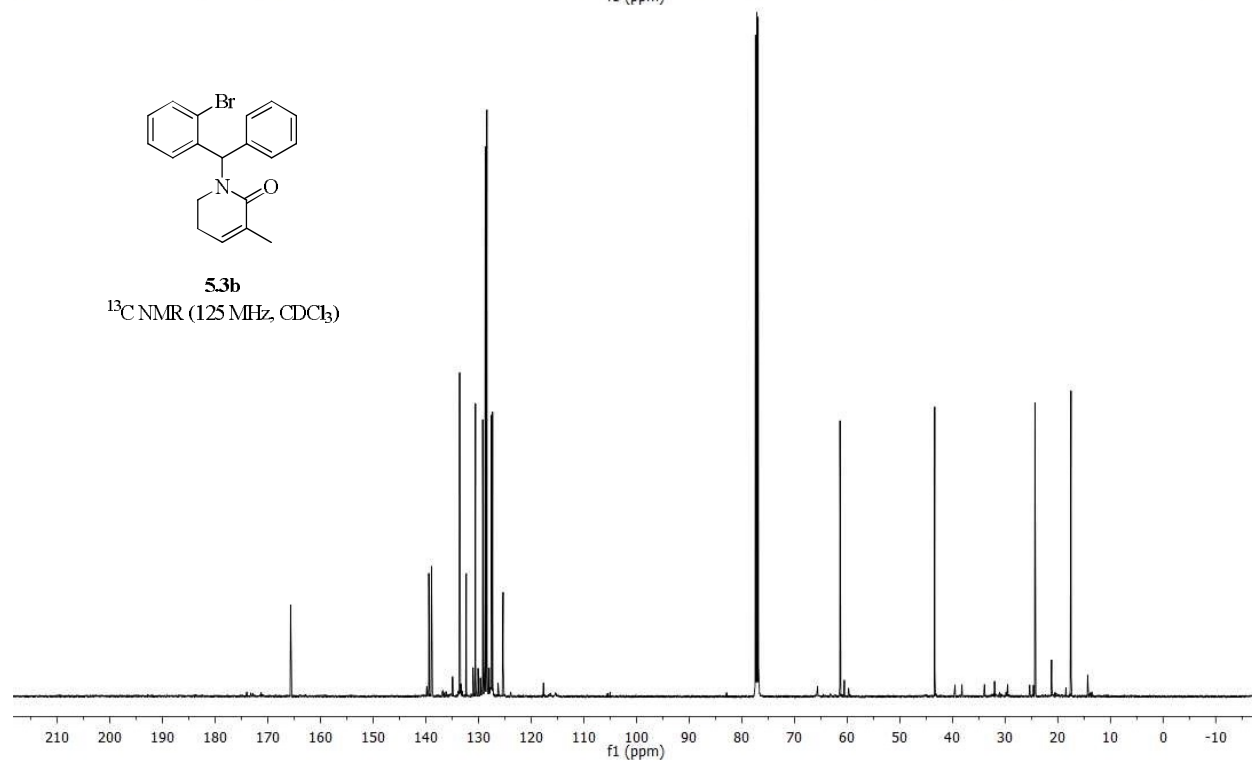
**5.3b**

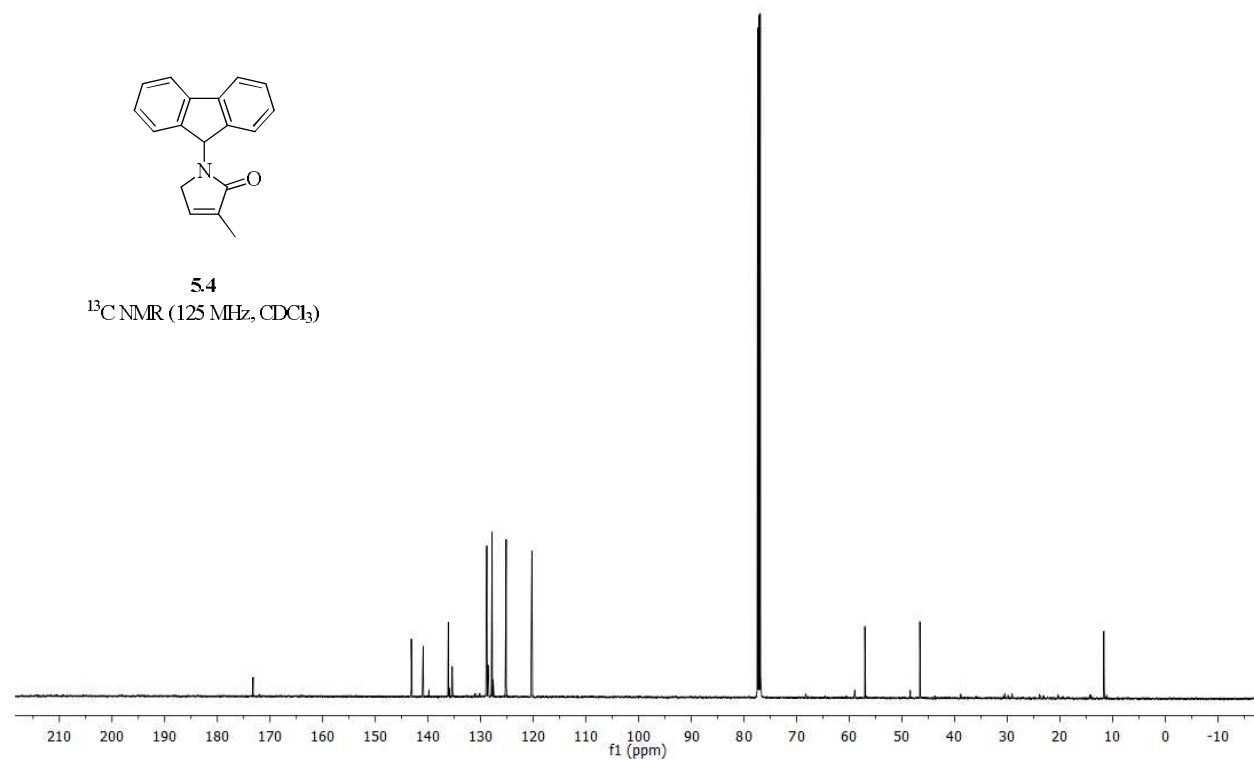
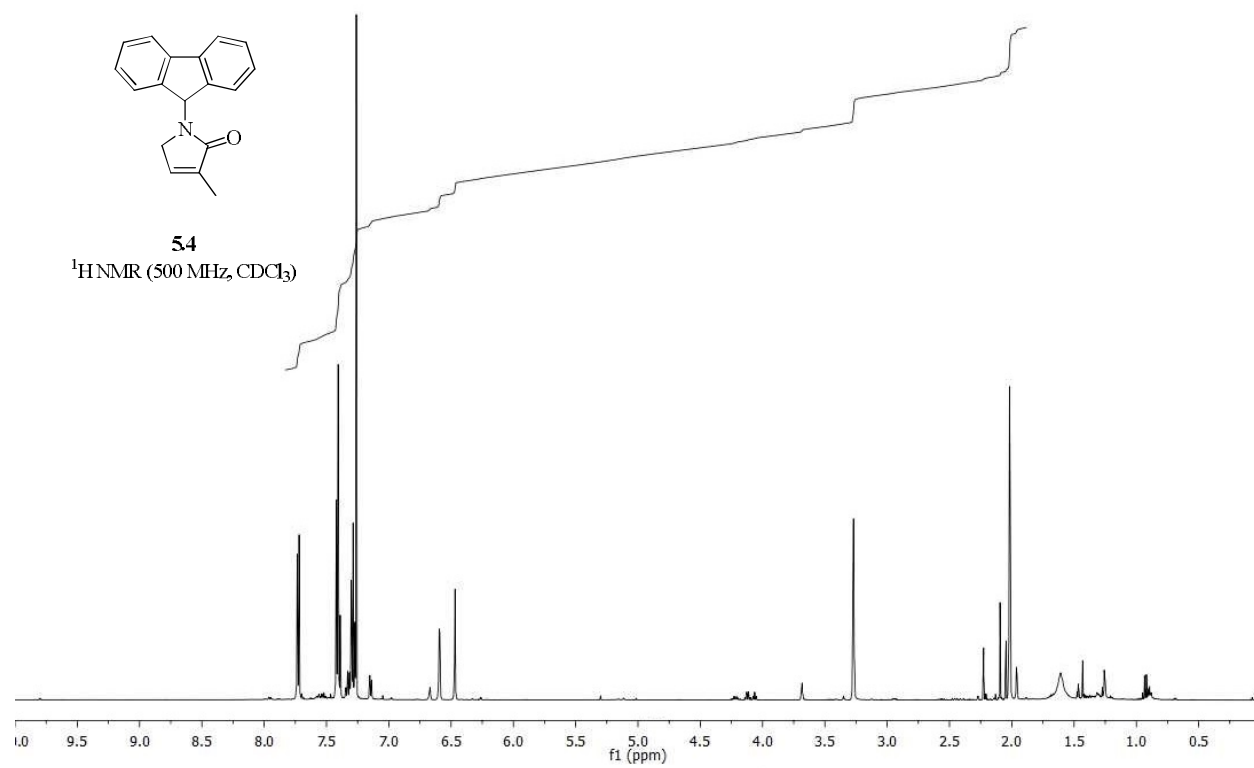
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



**5.3b**

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )





## Acknowledgment

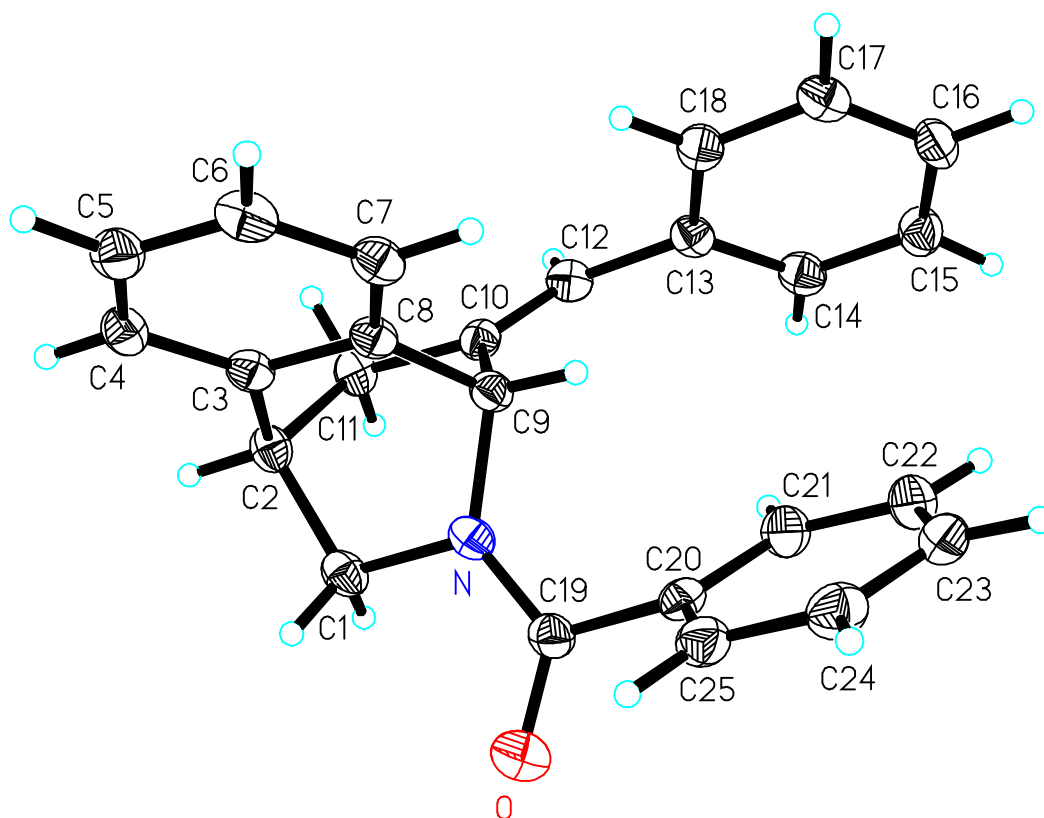
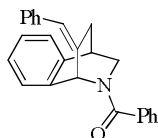
NMR assistance by Justin Douglas and Sarah Neuenswander.

GC-MS assistance by Todd Williams and Robert Drake

## GCMS purity analysis for compounds **4.4a-e**

The Gas Chromatography-Mass Spectrometric data were collected on an Agilent 6890N gas chromatograph eluting into a Quattro Micro GC mass spectrometer (Micromass Ltd, Manchester UK). An HP-5MS, 15 meter column with a 0.25" ID was used. The carrier gas was Helium using constant flow control set to 1.5 mL per minute. 1.0  $\mu$ L of sample was injected into the column with a 20:1 split ratio. The injector port temperature was 240 °C. The chromatographic conditions were as follows: The initial column temperature was 50 °C with a 1 minute hold after which the temperature was increased 25 °C/min to a final temperature of 300 °C and held for 2 minutes. EI ionization was used with ion energy of 70V. The mass range was 45 to 400 m/z with a 0.3 scan time and an inter scan delay time of 0.07 seconds.

## X-Ray Crystal Structure Report for Lactam **4.4a**



### Acknowledgment

This x-ray analysis was performed by Victor Day.

Table 1. Crystal data and structure refinement for C<sub>25</sub>H<sub>21</sub>NO.

Identification code	q94a
Empirical formula	C <sub>25</sub> H <sub>21</sub> N O
Formula weight	351.43

Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	Cc	
Unit cell dimensions	a = 12.0461(4) Å	$\alpha = 90^\circ$ .
	b = 17.2429(6) Å	$\beta = 93.888(2)^\circ$ .
	c = 8.6644(3) Å	$\gamma = 90^\circ$ .
Volume	1795.54(11) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.300 Mg/m <sup>3</sup>	
Absorption coefficient	0.610 mm <sup>-1</sup>	
F(000)	744	
Crystal size	0.21 x 0.19 x 0.09 mm <sup>3</sup>	
Theta range for data collection	4.48 to 68.47°.	
Index ranges	-12 ≤ h ≤ 14, -18 ≤ k ≤ 20, -10 ≤ l ≤ 10	
Reflections collected	8386	
Independent reflections	2622 [R(int) = 0.0237]	
Completeness to theta = 68.47°	95.1 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.888	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	2622 / 2 / 327	
Goodness-of-fit on F <sup>2</sup>	1.037	
Final R indices [I > 2σ(I)]	R1 = 0.0301, wR2 = 0.0799	
R indices (all data)	R1 = 0.0304, wR2 = 0.0802	
Absolute structure parameter	0.0(3)	
Largest diff. peak and hole	0.466 and -0.157 e.Å <sup>-3</sup>	

Table 2. Atomic coordinates (x 10<sup>4</sup>) and equivalent isotropic displacement parameters (Å<sup>2</sup>x 10<sup>3</sup>) for C25H21NO.

U(eq) is defined as one third of the trace of the orthogonalized U<sup>ij</sup> tensor.

	x	y	z	U(eq)
O	5448(1)	4050(1)	1412(2)	35(1)
N	4753(1)	3552(1)	3538(2)	22(1)
C(1)	5358(2)	4137(1)	4528(2)	23(1)
C(2)	4979(2)	4053(1)	6172(2)	22(1)
C(3)	3732(2)	4146(1)	6089(2)	21(1)
C(4)	3127(2)	4704(1)	6820(2)	23(1)
C(5)	1973(2)	4726(1)	6554(2)	27(1)
C(6)	1426(2)	4188(1)	5574(2)	26(1)
C(7)	2033(2)	3622(1)	4844(2)	23(1)
C(8)	3177(1)	3606(1)	5102(2)	20(1)
C(9)	3967(1)	3058(1)	4376(2)	20(1)
C(10)	4674(1)	2649(1)	5650(2)	19(1)
C(11)	5291(2)	3223(1)	6729(2)	23(1)
C(12)	4784(1)	1885(1)	5780(2)	22(1)
C(13)	4134(1)	1303(1)	4830(2)	21(1)
C(14)	4668(2)	734(1)	4003(2)	24(1)
C(15)	4053(2)	192(1)	3122(2)	27(1)
C(16)	2900(2)	195(1)	3081(2)	26(1)
C(17)	2366(2)	744(1)	3935(2)	24(1)
C(18)	2975(2)	1299(1)	4791(2)	23(1)
C(19)	4825(2)	3580(1)	1996(2)	22(1)
C(20)	4107(1)	3051(1)	981(2)	22(1)
C(21)	4230(2)	2246(1)	1015(2)	26(1)
C(22)	3570(2)	1784(1)	4(2)	29(1)
C(23)	2786(2)	2118(1)	-1030(2)	28(1)
C(24)	2652(2)	2918(1)	-1063(2)	29(1)
C(25)	3319(2)	3382(1)	-71(2)	26(1)

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Table 3. Bond lengths [Å] and angles [°] for C<sub>25</sub>H<sub>21</sub>NO.

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O-C(19)	1.236(2)
N-C(19)	1.345(2)
N-C(1)	1.484(2)
N-C(9)	1.497(2)
C(1)-C(2)	1.532(3)
C(1)-H(1A)	0.97(2)
C(1)-H(1B)	0.99(2)
C(2)-C(3)	1.507(2)
C(2)-C(11)	1.549(2)
C(2)-H(2)	0.989(19)
C(3)-C(4)	1.387(2)
C(3)-C(8)	1.403(2)
C(4)-C(5)	1.394(3)
C(4)-H(4)	0.95(2)
C(5)-C(6)	1.393(3)
C(5)-H(5)	0.97(2)
C(6)-C(7)	1.396(3)
C(6)-H(6)	1.00(2)
C(7)-C(8)	1.381(2)
C(7)-H(7)	0.98(2)
C(8)-C(9)	1.508(2)
C(9)-C(10)	1.521(2)
C(9)-H(9)	0.95(2)
C(10)-C(12)	1.328(2)
C(10)-C(11)	1.521(2)
C(11)-H(11A)	0.98(2)

C(11)-H(11B)	1.02(2)
C(12)-C(13)	1.487(2)
C(12)-H(12)	1.17(2)
C(13)-C(18)	1.394(3)
C(13)-C(14)	1.397(3)
C(14)-C(15)	1.388(3)
C(14)-H(14)	0.95(2)
C(15)-C(16)	1.388(3)
C(15)-H(15)	0.97(2)
C(16)-C(17)	1.386(3)
C(16)-H(16)	0.93(2)
C(17)-C(18)	1.389(2)
C(17)-H(17)	0.97(2)
C(18)-H(18)	0.94(2)
C(19)-C(20)	1.500(2)
C(20)-C(25)	1.393(2)
C(20)-C(21)	1.396(3)
C(21)-C(22)	1.392(3)
C(21)-H(21)	1.01(2)
C(22)-C(23)	1.383(3)
C(22)-H(22)	0.97(2)
C(23)-C(24)	1.389(3)
C(23)-H(23)	0.95(2)
C(24)-C(25)	1.390(3)
C(24)-H(24)	0.95(2)
C(25)-H(25)	0.95(2)
C(19)-N-C(1)	119.17(14)
C(19)-N-C(9)	125.99(14)
C(1)-N-C(9)	114.09(13)
N-C(1)-C(2)	107.93(14)



N-C(1)-H(1A)	108.5(12)
C(2)-C(1)-H(1A)	110.9(12)
N-C(1)-H(1B)	110.1(12)
C(2)-C(1)-H(1B)	110.5(12)
H(1A)-C(1)-H(1B)	108.9(18)
C(3)-C(2)-C(1)	107.71(13)
C(3)-C(2)-C(11)	109.46(14)
C(1)-C(2)-C(11)	107.21(14)
C(3)-C(2)-H(2)	112.2(11)
C(1)-C(2)-H(2)	106.7(11)
C(11)-C(2)-H(2)	113.3(10)
C(4)-C(3)-C(8)	119.71(15)
C(4)-C(3)-C(2)	127.24(15)
C(8)-C(3)-C(2)	113.01(14)
C(3)-C(4)-C(5)	119.47(16)
C(3)-C(4)-H(4)	116.9(14)
C(5)-C(4)-H(4)	123.6(14)
C(6)-C(5)-C(4)	120.58(17)
C(6)-C(5)-H(5)	117.9(12)
C(4)-C(5)-H(5)	121.5(12)
C(5)-C(6)-C(7)	120.03(17)
C(5)-C(6)-H(6)	121.3(12)
C(7)-C(6)-H(6)	118.6(12)
C(8)-C(7)-C(6)	119.27(16)
C(8)-C(7)-H(7)	122.2(13)
C(6)-C(7)-H(7)	118.5(13)
C(7)-C(8)-C(3)	120.94(15)
C(7)-C(8)-C(9)	126.58(15)
C(3)-C(8)-C(9)	112.45(14)
N-C(9)-C(8)	106.51(13)

N-C(9)-C(10)	105.94(13)
C(8)-C(9)-C(10)	109.03(13)
N-C(9)-H(9)	110.0(13)
C(8)-C(9)-H(9)	111.2(13)
C(10)-C(9)-H(9)	113.8(12)
C(12)-C(10)-C(11)	123.48(15)
C(12)-C(10)-C(9)	124.75(15)
C(11)-C(10)-C(9)	111.71(13)
C(10)-C(11)-C(2)	108.17(13)
C(10)-C(11)-H(11A)	110.0(12)
C(2)-C(11)-H(11A)	108.1(12)
C(10)-C(11)-H(11B)	108.4(11)
C(2)-C(11)-H(11B)	110.2(12)
H(11A)-C(11)-H(11B)	111.9(17)
C(10)-C(12)-C(13)	125.23(15)
C(10)-C(12)-H(12)	119.3(10)
C(13)-C(12)-H(12)	115.5(10)
C(18)-C(13)-C(14)	118.61(16)
C(18)-C(13)-C(12)	120.34(15)
C(14)-C(13)-C(12)	121.02(16)
C(15)-C(14)-C(13)	120.54(18)
C(15)-C(14)-H(14)	119.3(12)
C(13)-C(14)-H(14)	120.1(12)
C(16)-C(15)-C(14)	120.51(17)
C(16)-C(15)-H(15)	122.2(13)
C(14)-C(15)-H(15)	117.3(13)
C(17)-C(16)-C(15)	119.22(16)
C(17)-C(16)-H(16)	120.5(15)
C(15)-C(16)-H(16)	120.2(15)
C(16)-C(17)-C(18)	120.55(17)

C(16)-C(17)-H(17)	122.1(12)
C(18)-C(17)-H(17)	117.3(12)
C(17)-C(18)-C(13)	120.53(16)
C(17)-C(18)-H(18)	120.3(12)
C(13)-C(18)-H(18)	119.2(12)
O-C(19)-N	120.82(15)
O-C(19)-C(20)	120.01(15)
N-C(19)-C(20)	119.14(14)
C(25)-C(20)-C(21)	119.24(16)
C(25)-C(20)-C(19)	118.31(15)
C(21)-C(20)-C(19)	122.40(15)
C(22)-C(21)-C(20)	120.00(16)
C(22)-C(21)-H(21)	120.9(12)
C(20)-C(21)-H(21)	119.1(12)
C(23)-C(22)-C(21)	120.33(16)
C(23)-C(22)-H(22)	122.4(12)
C(21)-C(22)-H(22)	117.2(12)
C(22)-C(23)-C(24)	120.07(17)
C(22)-C(23)-H(23)	120.2(12)
C(24)-C(23)-H(23)	119.8(12)
C(23)-C(24)-C(25)	119.80(17)
C(23)-C(24)-H(24)	123.6(12)
C(25)-C(24)-H(24)	116.6(12)
C(24)-C(25)-C(20)	120.55(15)
C(24)-C(25)-H(25)	119.1(12)
C(20)-C(25)-H(25)	120.4(12)

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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for C<sub>25</sub>H<sub>21</sub>NO. The anisotropic displacement factor

exponent takes the form:  $-2\pi^2[ h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12} ]$

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{23}$	$U^{13}$	$U^{12}$
O	36(1)	32(1)	38(1)	3(1)	7(1)	-7(1)
N	19(1)	20(1)	25(1)	1(1)	1(1)	-3(1)
C(1)	17(1)	21(1)	30(1)	-1(1)	0(1)	-3(1)
C(2)	20(1)	20(1)	25(1)	-2(1)	-1(1)	0(1)
C(3)	22(1)	20(1)	21(1)	4(1)	1(1)	-2(1)
C(4)	26(1)	18(1)	25(1)	2(1)	1(1)	0(1)
C(5)	27(1)	22(1)	32(1)	4(1)	6(1)	3(1)
C(6)	19(1)	26(1)	33(1)	7(1)	-1(1)	0(1)
C(7)	23(1)	22(1)	23(1)	4(1)	-1(1)	-1(1)
C(8)	21(1)	19(1)	20(1)	4(1)	1(1)	-1(1)
C(9)	19(1)	19(1)	20(1)	0(1)	1(1)	-3(1)
C(10)	16(1)	23(1)	20(1)	-2(1)	2(1)	0(1)
C(11)	22(1)	22(1)	24(1)	-1(1)	-2(1)	0(1)
C(12)	18(1)	24(1)	23(1)	2(1)	0(1)	1(1)
C(13)	23(1)	18(1)	20(1)	4(1)	-1(1)	1(1)
C(14)	25(1)	21(1)	28(1)	4(1)	2(1)	1(1)
C(15)	32(1)	21(1)	27(1)	-2(1)	3(1)	2(1)
C(16)	32(1)	20(1)	24(1)	0(1)	-3(1)	-6(1)
C(17)	23(1)	25(1)	25(1)	6(1)	-3(1)	-3(1)
C(18)	28(1)	20(1)	21(1)	3(1)	1(1)	2(1)
C(19)	23(1)	17(1)	26(1)	2(1)	5(1)	3(1)
C(20)	22(1)	24(1)	20(1)	-1(1)	8(1)	0(1)
C(21)	27(1)	24(1)	28(1)	-1(1)	3(1)	2(1)
C(22)	35(1)	21(1)	31(1)	-4(1)	7(1)	0(1)
C(23)	30(1)	31(1)	22(1)	-4(1)	5(1)	-6(1)

C(24)	30(1)	35(1)	23(1)	4(1)	0(1)	0(1)
C(25)	32(1)	23(1)	23(1)	3(1)	5(1)	2(1)

Table 5. Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^{-3}$ ) for C<sub>25</sub>H<sub>21</sub>NO.

	x	y	z	U(eq)
H(1A)	6150(20)	4040(12)	4510(20)	23(5)
H(1B)	5194(18)	4667(13)	4120(20)	24(5)
H(2)	5363(16)	4464(11)	6800(20)	14(4)
H(4)	3536(19)	5061(13)	7470(30)	27(5)
H(5)	1524(18)	5104(12)	7060(20)	21(5)
H(6)	600(20)	4198(11)	5370(20)	24(5)
H(7)	1627(19)	3240(12)	4180(30)	26(5)
H(9)	3579(19)	2715(12)	3670(20)	21(5)
H(11A)	5056(18)	3162(12)	7780(30)	24(5)
H(11B)	6130(20)	3133(12)	6680(20)	25(5)
H(12)	5419(18)	1630(12)	6730(20)	26
H(14)	5454(19)	703(11)	4070(20)	16(4)
H(15)	4460(20)	-170(13)	2520(30)	28(5)
H(16)	2490(20)	-174(13)	2500(30)	30(6)
H(17)	1570(20)	742(11)	4010(20)	22(5)
H(18)	2609(18)	1677(11)	5350(20)	16(4)
H(21)	4810(19)	2006(12)	1770(20)	27(5)
H(22)	3708(18)	1231(12)	30(20)	23(5)
H(23)	2350(18)	1804(12)	-1730(20)	22(5)
H(24)	2110(18)	3176(11)	-1720(20)	21(5)
H(25)	3230(18)	3931(13)	-120(20)	25(5)

Table 6. Torsion angles [°] for C<sub>25</sub>H<sub>21</sub>NO.

C(19)-N-C(1)-C(2)	170.79(14)
C(9)-N-C(1)-C(2)	0.09(19)
N-C(1)-C(2)-C(3)	-56.69(17)
N-C(1)-C(2)-C(11)	61.03(17)
C(1)-C(2)-C(3)-C(4)	-119.59(17)
C(11)-C(2)-C(3)-C(4)	124.16(18)
C(1)-C(2)-C(3)-C(8)	58.13(17)
C(11)-C(2)-C(3)-C(8)	-58.12(18)
C(8)-C(3)-C(4)-C(5)	-0.6(2)
C(2)-C(3)-C(4)-C(5)	176.97(16)
C(3)-C(4)-C(5)-C(6)	0.6(2)
C(4)-C(5)-C(6)-C(7)	-0.2(3)
C(5)-C(6)-C(7)-C(8)	-0.2(2)
C(6)-C(7)-C(8)-C(3)	0.3(2)
C(6)-C(7)-C(8)-C(9)	-177.75(15)
C(4)-C(3)-C(8)-C(7)	0.2(2)
C(2)-C(3)-C(8)-C(7)	-177.75(15)
C(4)-C(3)-C(8)-C(9)	178.44(14)
C(2)-C(3)-C(8)-C(9)	0.53(18)
C(19)-N-C(9)-C(8)	-113.55(17)
C(1)-N-C(9)-C(8)	56.41(17)
C(19)-N-C(9)-C(10)	130.46(16)
C(1)-N-C(9)-C(10)	-59.58(16)
C(7)-C(8)-C(9)-N	121.06(17)
C(3)-C(8)-C(9)-N	-57.10(16)
C(7)-C(8)-C(9)-C(10)	-125.04(17)

C(3)-C(8)-C(9)-C(10)	56.80(16)
N-C(9)-C(10)-C(12)	-119.22(19)
C(8)-C(9)-C(10)-C(12)	126.51(19)
N-C(9)-C(10)-C(11)	58.08(17)
C(8)-C(9)-C(10)-C(11)	-56.19(18)
C(12)-C(10)-C(11)-C(2)	177.95(18)
C(9)-C(10)-C(11)-C(2)	0.6(2)
C(3)-C(2)-C(11)-C(10)	55.44(18)
C(1)-C(2)-C(11)-C(10)	-61.13(18)
C(11)-C(10)-C(12)-C(13)	175.07(16)
C(9)-C(10)-C(12)-C(13)	-7.9(3)
C(10)-C(12)-C(13)-C(18)	-57.1(3)
C(10)-C(12)-C(13)-C(14)	125.1(2)
C(18)-C(13)-C(14)-C(15)	2.0(2)
C(12)-C(13)-C(14)-C(15)	179.88(15)
C(13)-C(14)-C(15)-C(16)	-1.7(3)
C(14)-C(15)-C(16)-C(17)	-0.1(3)
C(15)-C(16)-C(17)-C(18)	1.7(2)
C(16)-C(17)-C(18)-C(13)	-1.3(2)
C(14)-C(13)-C(18)-C(17)	-0.5(2)
C(12)-C(13)-C(18)-C(17)	-178.38(15)
C(1)-N-C(19)-O	5.1(2)
C(9)-N-C(19)-O	174.64(16)
C(1)-N-C(19)-C(20)	-172.64(15)
C(9)-N-C(19)-C(20)	-3.1(2)
O-C(19)-C(20)-C(25)	-61.0(2)
N-C(19)-C(20)-C(25)	116.77(18)
O-C(19)-C(20)-C(21)	116.5(2)
N-C(19)-C(20)-C(21)	-65.7(2)
C(25)-C(20)-C(21)-C(22)	0.0(3)

C(19)-C(20)-C(21)-C(22)	-177.48(17)
C(20)-C(21)-C(22)-C(23)	-0.3(3)
C(21)-C(22)-C(23)-C(24)	-0.2(3)
C(22)-C(23)-C(24)-C(25)	1.0(3)
C(23)-C(24)-C(25)-C(20)	-1.4(3)
C(21)-C(20)-C(25)-C(24)	0.9(3)
C(19)-C(20)-C(25)-C(24)	178.44(17)

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Symmetry transformations used to generate equivalent atoms: